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The New England Journal of Medicine

Formerly The Boston Medical and Surgical Journal
Established 1828

Volume 222 JUNE 13, 1940 Number 24

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TENNESSEE STATE MEDICAL ASSOCIATION

Owned and Published by the Massachusetts Medical Society

Published weekly in Boston at 8 Fenway. Domestic, $6 per annum, 25c per copy; Canada, $7.04; Foreign, $8.52.
Entered as second-class matter, November 16, 1932, at the post office at Boston, Mass., under the Act of March 3, 1879.
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VOLUME 222 JUNE 13, 1940 NUMBER 24

AGNOGENIC MYELOID METAPLASIA OF THE SPLEEN*

A Syndrome Simulating Other More Definite Hematologic Disorders

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BOSTON

IT IS well recognized that a varying degree of extramedullary myelopoiesis occurs in a wide variety of pathologic conditions. It has, for example, been seen in association with carcinoma metastatic to bone; it is not infrequent in certain infectious states such as scarlet fever; and it has been noted in generalized sepsis, tuberculosis of the spleen and in areas of pathologic calcification and ossification.[1] Under such circumstances, the process is of pathological interest only, for the primary underlying disease is usually patently manifest and the ectopic blood formation is minimal in amount. In myelogenous leukemia, of course, the extramedullary myelopoiesis reaches its greatest height. The liver, spleen, lymph nodes and many other organs are invaded by immature and abnormal cells of the granulocyte series. Here again, however, the process is of secondary interest to the clinician. It is true that the body as a whole is widely involved and that thereby irreparable damage is done, but the fundamental disorder is usually clearly apparent, and the diagnostic, therapeutic and prognostic implications are therefore obvious.

At this time we particularly wish to draw attention to another class of patients with myeloid metaplasia in whom this abnormal process assumes major proportions, and in whom it may therefore be responsible for serious errors in diagnosis.

In general, it may be said that these patients show a slowly progressive enlargement of the spleen, and, over a long period of time, present a blood picture which simulates that of myelogenous leukemia, or, more rarely, that of acquired hemolytic jaundice. The fact that splenectomy on the one hand or irradiation of the spleen on the other is rarely of material benefit and is often followed by serious results indicates clearly the importance of recognizing this symptom-complex and separating it distinctly from those conditions which it may simulate. We have designated this type of myeloid metaplasia of the spleen as "agnogenic."*

The literature on extramedullary myelopoiesis is large and confusing. We refer here to two papers only. Hickling[2] has referred to this type of myeloid metaplasia as "chronic non-leukemic myelosis." He presents a review of the cases in the literature and adds 7 of his own. Hickling says, "The diagnosis of chronic non-leukemic myelosis depends on the finding of immature red and white cells in the circulating blood without the great increase in the total number of leukocytes characteristic [*sic*] of leukemia in a patient with massive enlargement of the spleen." As will be apparent from the present study, the diagnosis is by no means so easy; indeed, without both bone-marrow biopsy and splenic puncture, it is doubtful whether the diagnosis can be established during life with any degree of certainty.

Hickling's patients showed a progressive enlargement of the spleen and to a less extent of the liver, the constant presence of immature myeloid cells and nucleated red cells in the peripheral blood, basophilia, an increased indirect van den Bergh reaction in the blood serum and spontaneous hemorrhages. In 2 cases there was x-ray evidence of osteosclerosis, and Hickling lays much emphasis on this point, despite the fact that no histological evidence for such sclerosis was forthcoming in his series.

The early symptoms in his cases included abdominal pain, purpura and especially epistaxis or hematemesis. The course of the disease was slow.

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*This word, derived from the Greek, was suggested by Dr. Robert M. Green, and means "of unknown or uncertain etiology."

Of his 7 patients, 5 were alive and in reasonably good health from two to seventeen years from the date of the first symptom. Two patients died, one following a short febrile illness thirteen years after onset, and the other following ligation of the splenic pedicle nineteen years after the first symptoms. Hickling very properly warns against splenectomy, and points out that of the 27 patients reported in the literature who were subjected to this procedure, 15 died within a few days of operation.

Histological examinations were made in only 3 of Hickling's cases. In his second case, a splenculus removed at operation showed myeloid metaplasia of the pulp without involvement of the Malpighian bodies. In his third case, there was myeloid metaplasia of the spleen and liver and an "intensely active" marrow was found in the lower end of the femur. In his fourth case, he found myeloid metaplasia of the spleen, liver, kidneys, lymph nodes and skin. The bone marrow appeared normal.

Vaughan and Harrison[3] have described 2 somewhat similar cases in which there was splenomegaly, increased red-cell fragility, a leukemoid blood picture and eventually a profound anemia. In both cases there was an initial polycythemia. In both there were osteoporosis and extensive fibrosis of the bone marrow. They suggest that "polycythemia vera, megakaryocytic leukemia and myelosclerosis with leukoerythroblastic anemia form a group of closely related conditions." Vaughan, too, warns that "if sclerosis of the marrow is present, x-ray or radium treatment would appear to be contraindicated."

We here report 10 cases proved by histological examinations to have had extensive myeloid metaplasia, especially of the spleen. In all, the onset was insidious and the course slow. In 9, the clinical and hematologic picture simulated that of myelogenous leukemia. One case was erroneously diagnosed as hemolytic jaundice. In all cases, foci of young myeloid cells and megakaryocytes were present in the enlarged and fibrosed spleen and this organ was the chief, though not the only, site of the ectopic blood formation. In the majority of these spleens were found, in addition, isolated clusters of immature red blood cells.

In 3 cases irradiation was applied to the spleen; two of these patients died within a few weeks; the third was not materially helped and died two years later. Three splenectomies were performed. Two of the patients died within six weeks; the third was not improved and died a year later of generalized sepsis.

Autopsies were performed on 6 of the 10 patients. Splenic punctures and bone-marrow biopsies were carried out on 3 of the remaining cases, and splenectomy on 1.

It is obvious that from a pathological as well as a clinical standpoint the disease from which this symptom complex must most often be differentiated is chronic myelogenous leukemia.

The spleen in agnogenic myeloid metaplasia shows fibrosis varying in degree from slight to marked. Occurring in isolated foci are found hematopoietic cells of various types. Myelocytes and other early forms of the granulocytic series are constantly found. Collections of nucleated red cells or earlier forms of the same series may be present. As a rule megakaryocytes are found, and they are often present in large numbers. The Malpighian corpuscles are preserved, although they may contain an occasional myelocyte or megakaryocyte. Hemosiderin in macrophages may be present, often in considerable amount.

In contrast, a spleen from a case of leukemia that has received no irradiation therapy is characterized by a marked diffuse infiltration by immature cells of the granulocytic series. Young red cells may or may not be present and are seldom a prominent feature. Megakaryocytes are usually seen. The Malpighian corpuscles are as a rule completely obliterated. Infarcts are extremely common. If a case has been irradiated, the histologic picture in the spleen is complicated by the appearance of fibrosis, which may be considerable in amount. In making a differential diagnosis between myeloid metaplasia and myelogenous leukemia on such a spleen, one must depend mainly on the persistence or loss of the Malpighian corpuscles and the absence or presence of infarcts. Thus it is evident that a positive differential diagnosis can usually be made on a section of spleen, but not on a specimen obtained by splenic puncture alone; for in the latter only the separate cytological elements can be studied and not the general architecture of the organ. The evidence obtained from a splenic puncture may, however, be combined with that obtained from bone-marrow and hematological studies to make a definite diagnosis.

The bone marrow from patients with leukemia shows a diffuse infiltration of immature cells of the granulocytic series and a marked decrease in the red-cell series. Fat tissue is usually absent. In myeloid metaplasia, on the other hand, the picture varies greatly. The marrow may appear normal, aplastic, hyperplastic or fibrotic, but in no instance have we seen a change which could be confused with that of leukemia.

The liver in leukemia is characterized by extensive infiltration of the portal areas by young gran-

ulocytes with, in addition, numerous similar cells in the sinusoids. In myeloid metaplasia the picture varies considerably, but usually consists of focal collections in the sinusoids of cells of the granulocytic or red-cell series. Megakaryocytes are commonly present.

The lymph nodes in leukemia usually show a diffuse infiltration of the sinuses and cords with immature granulocytes. Foci of red-cell formation and megakaryocytes may or may not be present. In myeloid metaplasia, isolated collections of young granulocytes, immature red cells and megakaryocytes may occur. The process, however, is not diffuse as it is in leukemia.

In leukemia, there is frequently an infiltration of many other organs, such as the kidney and heart. In myeloid metaplasia, on the other hand, the occurrence in these organs of hematopoietic cells is very rare and they are never present in a significant number.

In brief, then, the main difference between the histological picture of leukemia and that of myeloid metaplasia is the diffuse, neoplastic-like infiltration in the former, as contrasted with the localized and focal aggregations of hematopoietic cells in the latter. It should be emphasized once more that the bone marrow in myeloid metaplasia never shows the histologic features usually considered diagnostic of leukemia.

Thus it is clear that the pathological differential diagnosis between leukemia and myeloid metaplasia can be made without difficulty on autopsy material or on a spleen that can be examined histologically. It is equally clear that a specimen removed by splenic puncture can merely furnish information as to the presence or absence of hematopoietic cells, and that a differential diagnosis from leukemia cannot be made by this procedure alone. The findings of such myeloid cells in a splenic puncture together with histologic evidence that the bone marrow is not leukemic is, however, sufficient for a diagnosis of myeloid metaplasia.

The following cases illustrate the clinical and pathologic characteristics of the condition.

Case 1 (No. 745,095). A. M., a 63-year-old woman, was admitted to the hospital on April 18, 1934. For 8 weeks she had grown progressively weaker and had suffered from increasing dyspnea, palpitation and nausea. Six weeks before entry she had noticed that her scleras and skin were markedly yellow. One week before admission she had fainted.

Her past history was essentially negative, except that she had been "pale" all her life, and for 6 years prior to entry had noticed a slight though definite yellowish tinge to her skin. The family history was irrelevant. In particular, none of the siblings had had jaundice.

Physical examination disclosed a pale, obese and jaundiced woman. Both the scleras and skin were definitely icteric. The mucous membranes were pale; the tongue appeared normal. The heart was enlarged 1 cm. to the left of the midclavicular line, and there was a harsh blowing systolic murmur over the entire precordium. The liver was just palpable on inspiration; the spleen was felt 6 cm. below the costal margin.

Both urobilin and urobilinogen tests on the urine were strongly positive. The stools showed the presence of bile and occult blood. The red-cell count was 820,000, the hemoglobin 20 per cent (Sahli) or 3.12 gm. per 100 cc., and the white-cell count 27,000, with 80 per cent polymorphonuclears, 10 per cent myelocytes, 2 per cent stem cells, 6 per cent lymphocytes and 2 per cent monocytes. There were marked poikilocytosis and anisocytosis, and many nucleated red blood cells were seen in the smear. There were 38 per cent reticulocytes. The hematocrit reading was 11.4 per cent. The mean corpuscular volume was 138.8 cu. microns, the mean corpuscular hemoglobin concentration 27.4 per cent and the mean corpuscular hemoglobin 38 micro-microgm. Blood platelets were normal in number and appearance. The icteric index was 50. The indirect van den Bergh reaction was positive. Gastric analysis showed no free hydrochloric acid even after the administration of histamine. Fragility tests showed a moderate increase in the susceptibility of the red cells to hemolysis by hypotonic solutions of sodium chloride. Hemolysis began at 0.54 and was complete at 0.30.

A tentative diagnosis of acquired hemolytic jaundice was made.

On May 10, a sternal bone-marrow biopsy (JP-108) showed numerous stem cells, erythroblasts, normoblasts and nucleated red cells. A moderate number of granulocytes and megakaryocytes were also present. These findings, while not diagnostic, were considered consistent with hemolytic jaundice. Following a blood transfusion, the red-cell count rose to 2,100,000, the hemoglobin to 50 per cent (Sahli) or 7.8 gm. per 100 cc., and the reticulocytes to 45 per cent.

On June 12, 2 months after admission, the fragility of the red cells had further increased, hemolysis beginning at 0.66 and being complete at 0.28. The icteric index coincidentally fell to 17. Two further transfusions of blood were given. The patient's strength and general condition improved and on August 30, a splenectomy was performed. The spleen (S-34-3007) weighed 1240 gm. The capsule was smooth and the consistence firm. On section the cut surface was uniformly dark red and neither the Malpighian corpuscles nor trabeculae were prominent. Microscopically there was diffuse fibrosis. Focal areas of myelocytes with rare adult granulocytes were prominent. Numerous foci of red-cell formation were present. In addition, scattered throughout the organ were a large number of megakaryocytes. The Malpighian corpuscles were for the most part well preserved. The histologic picture in no way suggested that usually seen in hemolytic jaundice and often considered diagnostic of that disease.[4] The patient died 3 days after operation.

Autopsy (A-34-494) showed generalized peritonitis, chronic cholecystitis with cholelithiasis, nephrolithiasis, and hepatomegaly. The liver weighed 2050 gm. and microscopically showed hemosiderosis of a moderate degree and some fat in the liver cells. The vertebral, sternal and mid-femoral marrows were all hyperplastic, and all series of blood cells were well represented, with normal maturation. No lymph nodes were examined.

Comment. Here, then, was a patient who, over a period of at least 6 years, had had slight jaundice and weakness, and who entered the hospital with the clinical and labora-

tory findings usually considered diagnostic of hemolytic jaundice. Yet the seemingly justifiable splenectomy was followed shortly by death, and the spleen failed to show the lesions of this disease, but revealed instead only marked myeloid metaplasia.

Case 2 (No. 566,172). E. H., a 52-year-old man, entered the hospital on July 2, 1928. Twelve years prior to entry he began to feel generally weak and "sick." At the same time there developed on the right great toe and on the dorsum of the left foot small areas of gangrene, which cleared gradually when treated with "dilute carbolic acid," in spite of the fact that amputation had been deemed necessary by an eminent specialist in vascular diseases. At the same time, the patient was told that his blood was "too thick," and he was advised to follow a special diet to remedy this defect. Shortly thereafter he noticed that his hands and feet constantly felt cold. The general weakness gradually increased, and in 1925 he was sufficiently ill to be confined to bed for a period of 2 months. His weakness had become extreme and he was slightly dyspneic, even at rest. It was at this time that the enlarged spleen was first noted.

The past history was uneventful, except that he had had malaria at the age of 18.

On entry to the hospital in 1928, physical examination showed a moderate degree of pallor of the mucous membranes. There was no lymphadenopathy. The lungs were clear. The heart was normal in size, but the sounds were of poor quality and there were many ventricular extrasystoles. The blood pressure was 120/70; the peripheral vessels were thickened and sclerotic. The abdomen was markedly distended and was almost filled by the enormously enlarged liver and spleen, the former reaching to the level of the umbilicus, the latter descending into the pelvis. Both organs were extremely hard.

The red-cell count was 3,400,000, the hemoglobin 83 per cent (Sahli) or 12.95 gm. per 100 cc., and the white-cell count 23,700, with 79 per cent polymorphonuclears, 6 per cent metamyelocytes, 7 per cent myelocytes, 5 per cent lymphocytes and 3 per cent monocytes. The platelets were normal. X-ray films of the long bones showed no abnormalities. The basal metabolic rate was +47 per cent, and a blood Hinton test was positive. Careful questioning revealed no history of luetic infection.

A diagnosis of myelogenous leukemia was made, and 200 r was given over the spleen. As a result of this small dose of x-ray, the white-cell count dropped to 8200, the differential count remaining essentially the same, and the basal metabolic rate fell to +19 per cent. Neither the liver nor the spleen decreased in size. Further x-ray treatment was withheld, and the patient left the hospital somewhat disgruntled because he had not had his "full share" of irradiation.

He returned, however, 4 years later and was readmitted on May 12, 1932, again complaining of weakness, which had become so marked that he was unable to work. In the 4 years since his discharge he had had a number of brisk nosebleeds, and latterly had noted edema of the ankles toward the end of the day. He had received no specific therapy.

At the time of the second admission the patient was found to be dyspneic, even at rest. There had been considerable weight loss. The liver and spleen were still grossly enlarged and very hard. The red-cell count was 1,900,000, the hemoglobin 44 per cent (Sahli) or 6.86 gm. per 100 cc., and the white-cell count 6300, with 50 per cent polymorphonuclears, 19 per cent myelocytes, 8 per cent premyelocytes, 2 per cent stem cells, 6 per cent monocytes and 15 per cent lymphocytes. The platelets were definitely diminished in number and 5 nucleated red cells were seen on counting 100 white cells.

On May 16 200 r was given to the spleen, followed by a severe reaction with dizziness, vomiting, great weakness and a severe nosebleed. On May 23 another dose of 200 r was given over the spleen, with marked diminution in its size but very little amelioration of symptoms. Physical examination revealed the presence of ascites, and 800 cc. of thin, blood-tinged fluid was withdrawn from the peritoneal cavity. The patient failed rapidly. The red-cell count fell to 1,070,000, the hemoglobin to 25 per cent (Sahli) or 3.9 gm. per 100 cc., and the white-cell count to 3050, with the differential count essentially as before. The patient died June 27, 1932, 16 years after the first symptom of his disease and 5 weeks after his final x-ray therapy.

Autopsy (PA-32-65) showed a small amount of clear fluid in both pleural cavities and fibrous adhesions at both lung bases. The heart was normal. In the peritoneal cavity was 900 cc. of bloody fluid. The spleen weighed 4600 gm. and cut with greatly increased resistance. The liver weighed 4400 gm., and similarly was very firm. There was definite enlargement of the mediastinal, paraaortic and mesenteric nodes. Grossly the bone marrow appeared normal.

Microscopically the spleen showed marked fibrous thickening of the capsule and pulp. There were many isolated foci of myelocytes. Nucleated red cells were numerous, but less mature forms were few. Megakaryocytes were rare. Phagocytosis of red cells by macrophages was a prominent feature. The Malpighian corpuscles were intact. In the liver, there were scattered immature cells of the granulocytic series in the sinusoids. Neither nucleated red cells nor megakaryocytes were present. The mediastinal and abdominal lymph nodes contained isolated foci of stem cells and myelocytes. Numerous nucleated red cells were present, and a few clumps of erythroblasts. There were many megakaryocytes. The lymph sinuses contained a few macrophages filled with red cells. The vertebral bone marrow showed a considerable degree of fibrosis. A few stem cells and myelocytes were present. There were large numbers of nucleated red cells and rare less adult forms. Megakaryocytes were few. A moderate number of macrophages containing numerous red cells were noted. The histological picture was, therefore, in no way suggestive of leukemia, and what little activity remained appeared to be confined mainly to the red-cell series.

Comment. This patient for many years had a greatly enlarged liver and spleen and was found to have a peripheral blood picture very suggestive of myelogenous leukemia. Apparent confirmation of this diagnosis was found in the elevated basal metabolism. Yet a very small amount of radiation produced a rather marked fall in the white-cell count, and subsequent moderate irradiation to the spleen was followed by rapidly developing anemia and death. Autopsy showed extramedullary myeloid metaplasia of the spleen and a fibrotic bone marrow. There was no evidence of leukemia.

Case 3 (No. H.17.199.93). W. R., a 60-year-old man, was first seen on May 2, 1917. For 20 years he had complained of postprandial distress in the left upper quadrant; for "many years" he had noticed a mass in the same region. For 12 months prior to entry he had felt tired and worn out. Six months later his own doctor had substantiated the fact that his spleen was enlarged.

The past and family histories were irrelevant.

On entry to the hospital, physical examination was es-

sentially normal, except that the liver was just palpable on inspiration and the spleen extended 7 cm. below the umbilical line on quiet respiration.

The red-cell count was 4,830,000, the hemoglobin 90 per cent (Sahli) or 13.9 gm. per 100 cc., and the white-cell count 13,100, with 70 per cent polymorphonuclears, 10 per cent myelocytes, 2 per cent stem cells, 4 per cent monocytes and 14 per cent lymphocytes. Five nucleated red cells were seen while counting 100 white cells, and there was marked anisocytosis, poikilocytosis and polychromatophilia. The platelets were greatly decreased in number. A diagnosis of myelogenous leukemia was made, and 6120 mc. hr. of radium was applied over the spleen at a distance of 5 cm., with 5 mm. of lead screening. Five days later the hemoglobin had fallen to 78 per cent, and the white-cell count to 6000. The differential count was essentially as before. The spleen was slightly but definitely smaller than on admission.

No further therapy was undertaken, but on June 7, 1 month after the initial radium treatment, the red-cell count had fallen to 1,700,000, the hemoglobin to 35 per cent and the white-cell count to 4000. A differential count revealed 54 per cent polymorphonuclears, 14 per cent myelocytes, 14 per cent stem cells and 18 per cent lymphocytes. The reticulocytes were but 0.1 per cent. The platelets had become still further reduced in number. Definite jaundice was noted for the first time. The spleen continued to recede, but the patient, after a short interval of slightly improved health, failed rapidly and died on July 19, 1917, 6 weeks after radium treatment.

Autopsy (H-A-17-85) showed the spleen extending to the umbilicus and weighing 2200 gm., and the liver reaching 6 cm. below the costal margin and weighing 2700 gm. There was no enlargement of the lymph nodes in any region. Microscopically the spleen showed a marked diffuse fibrosis. Fairly numerous foci of stem cells, myelocytes and more adult granulocytes were present. There was no red-cell formation and there were no nucleated red cells. A considerable number of megakaryocytes were noted. The Malpighian corpuscles were preserved, but were diminished in size and often contained an occasional myelocyte. There were a moderate number of lymphocytes and plasma cells in the pulp, and in addition a considerable number of hemosiderin-laden macrophages. The sinusoids of the liver contained a moderate number of myelocytes and megakaryocytes, but no nucleated red cells. The bone marrow from the vertebrae, sternum, femur and tibia was almost completely aplastic, with but a few isolated cells of the granulocytic series present.

Comment. This case also presented, when first seen, the clinical and hematologic features not inconsistent with a diagnosis of myelogenous leukemia. Irradiation to the spleen, however, was followed, as in Case 2, by rapid decline and early death. Autopsy showed an aplastic, fatty marrow and marked myeloid metaplasia of the spleen. It seems not improbable that in this case and in the preceding one the greatest part of the blood formation was taking place in the spleen, and that irradiation of this organ with consequent destruction of immature cells led to a rapidly developing anemia, leukopenia and death.

Case 4 (No. T-959). L. J., a 51-year-old white woman, was admitted to the hospital on September 22, 1931. In 1901 she had had tertian malaria. In 1906 she had had a severe attack of jaundice associated with anorexia, vertigo, headache and vomiting. This illness lasted for 2 months, and in the next 17 years she had three other similar episodes. In 1915 she was operated on for acute appendicitis. No mention of the spleen was made in the operative notes, but it was stated that the ovaries were underdeveloped, and subsequently she ceased to menstruate. In 1928, eight years prior to admission, the patient suffered from a profuse hemorrhage following the extraction of an abscessed tooth. In 1936 she vomited a large amount of blood on two occasions. An abdominal exploration was done. A gastric ulcer was said to have been found and a posterior gastroenterostomy was performed. In 1929 the patient complained of soreness of the tongue and loss of sensation of taste. From that time on, she did not feel well and complained of attacks of dizziness and vomiting.

The family history was irrelevant.

Physical examination on entry to the hospital in 1931 showed a middle-aged, pale woman in no apparent distress. There was no jaundice.The tongue was markedly atrophic and somewhat redder than normal. The spleen was found 4 cm. below the costal margin. The liver could not be felt. The red-cell count was 5,300,000, the hemoglobin 57 per cent (Sahli) or 8.89 gm. per 100 cc., and the white-cell count 28,500, with 70 per cent polymorphonuclears, 1 per cent metamyelocytes, 10 per cent myelocytes, 2 per cent stem cells, 11 per cent lymphocytes, 3.5 per cent monocytes and 2.5 per cent basophils. Five nucleated red blood cells were seen while counting 100 white cells. The reticulocytes were 5 per cent. The platelets were greatly increased, and many nucleated reds were seen in the smear. Gastric analysis showed no free hydrochloric acid even after the administration of histamine, and the icteric index was 9. The red-cell fragility began at 0.52 and was complete at 0.24.

A diagnosis of early myelogenous leukemia or atypical hemolytic jaundice was made, and the patient was put on massive doses of iron and ammonium citrate. Possibly as a result of this therapy the red-cell count rose to 7,600,000 and the hemoglobin to 110 per cent (Sahli) or 17.16 gm. per 100 cc. The white-cell count remained elevated, and the smear continued to show a definite though varying per cent of myelocytes, myeloblasts and nucleated red cells.

On December 9 the red-cell count was 7,680,000, the hemoglobin 104 per cent (Sahli) or 16.22 gm. per 100 cc., and the white-cell count 28,000, with 80 per cent polymorphonuclears, 3 per cent myelocytes, 1 per cent stem cells, 3 per cent basophils, 1 per cent monocytes, and 12 per cent lymphocytes. The platelets were markedly increased in number.

A biopsy (S-33-407) of the sternal marrow in February, 1933, showed patchy fibrosis. In the fibrotic areas, hematopoietic cells were few. Elsewhere the hematopoietic tissue was cellular and was composed of the granulocytic series and numerous megakaryocytes. Red-cell formation was comparatively slight. The patient continued to complain of vague paresthesias of the hands and feet, sore tongue and malaise, but her general condition remained fairly good.

In the latter part of 1932, the immature white cells in the peripheral blood became more numerous. On October 17, 1932, the red-cell count was 5,320,000, the hemoglobin 91 per cent (Sahli) or 14.20 gm. per 100 cc., and the white-cell count 9700, with 81 per cent polymorphonuclears, 3 per cent eosinophils, 1 per cent basophils, 14 per cent myelocytes and 1 per cent stem cells. Five nucleated red cells and 1 normoblast were seen in counting 100 white blood cells. The mean corpuscular volume was 86.2 cu. microns, the mean corpuscular hemoglobin concentration 32.3 per cent, the mean corpuscular hemoglobin 26.7 micromicrogm. and the hematocrit reading 45.9 per cent.

In November, 1935, the patient developed generalized joint pains, and x-ray films showed some hypertrophic arthritis about the right knee joint. She had failed con-

siderably in strength. The peripheral blood picture remained essentially as before, and the spleen was now palpable nearly to the umbilicus and was very hard in consistence.

The course of the disease slowly continued to advance and early in April, 1937, the patient had an attack of very severe pain in the right great toe, associated with marked redness and tenderness. The blood uric acid was 4.2 mg. per 100 cc. The pain subsided without specific therapy in the course of a week.

In June, 1938, a second sternal bone-marrow biopsy (S-38-1753) was performed. The bone marrow showed a greater degree of fibrosis than that seen in the first biopsy specimen. Scattered myelocytes, polymorphonuclear leukocytes and megakaryocytes were present, but were few in number. No red-cell formation was evident.

From this time on the patient's condition became progressively worse. There were no further hemorrhages, yet by January, 1939, the red-cell count had fallen to 3,700,000 and the hemoglobin to 50 per cent (Sahli) or 7.80 gm. per 100 cc. The white-cell count was 16,500, with 51 per cent polymorphonuclears, 2 per cent basophils, 3 per cent metamyelocytes, 13 per cent myelocytes, 4 per cent stem cells, 8 per cent monocytes and 19 per cent lymphocytes. The red-cell diameter was 6.84 microns. Forty-six nucleated red cells and 3 normoblasts were seen in counting 100 white cells. The platelets were markedly decreased in number. At this time, a splenic puncture was done and large numbers of myelocytes, premyelocytes, stem cells, nucleated red cells, normoblasts, erythroblasts and megakaryocytes were found.

Comment. This patient has shown for a period of at least 8 years features suggestive of myelogenous leukemia, namely an enlarged spleen, an elevated white-cell count and the presence in the peripheral blood of notable numbers of myelocytes, nucleated red cells and occasional stem cells. Certain findings such as the slightly increased red-cell fragility and the subclinical icterus were reminiscent of hemolytic jaundice. At one period when the red-cell count was over 7,000,000 polycythemia vera was considered as a distinct diagnostic possibility. Yet on two occasions bone-marrow biopsy failed to substantiate any of these diagnoses and splenic puncture revealed the presence of myeloid metaplasia. The onset of the disease was insidious; indeed, it is difficult to state with any degree of assurance when the condition started, though it is probable that the profuse hemorrhage following a tooth extraction 16 years previously should be taken as the first evidence of its existence.

In view of the disastrous results of splenectomy in Case 1, which had been diagnosed as hemolytic jaundice, and the apparently unfortunate effects of irradiation in Cases 2 and 3, which had erroneously been diagnosed as myelogenous leukemia, it is perhaps fortunate that this patient was treated symptomatically only.

Discussion

From a clinical and hematological point of view, these cases of agnogenic myeloid metaplasia of the spleen are most frequently confused with myelogenous leukemia in the subleukemic phase. More rarely they simulate classical myelogenous leukemia with comparatively high total white-cell counts. Still more rarely acquired hemolytic jaundice is imitated. In view of the apparent wisdom of treating these cases symptomatically only, the question naturally arises as to how they may be distinguished during life from these other more definite clinical entities. It is already apparent that such differentiation can, with assurance, be made only by combined hematological, clinical and pathological studies.

The total number of white cells in the peripheral blood varies, though it is usually moderately increased. Varying numbers of myelocytes and stem cells constantly occur in the peripheral blood, but the hematologic hiatus so suggestive of acute leukemia is not seen. The peripheral blood picture by itself is not distinctive.

The anemia, which may be normocytic, microcytic or macrocytic, varies in degree. It is usually moderate, rarely extreme. Except in those cases simulating hemolytic jaundice, the reticulocytes are not greatly increased. Nucleated red cells and more rarely normoblasts are found almost constantly in the peripheral blood stream. In certain cases some degree of polycythemia may exist in the early stages of the disease. It is possible that some cases of so-called polycythemia may actually belong in this class. The platelets may be increased, normal or decreased. The onset is insidious, the course slowly progressive.

The commonest symptoms are weakness, joint pains, anorexia, abdominal pain, epistaxis and loss of weight. The spleen is enlarged, often greatly so, and the liver is frequently increased in size. Both organs are of very firm consistence. Generalized lymphadenopathy does not occur. Slight jaundice is common.

During life, the condition may be suspected when a patient with a large spleen has had, over a considerable period of time, a subleukemic peripheral blood picture, together with occasional nucleated red cells in the smear. This suspicion becomes a probability if the spleen is very large and hard, slight jaundice is present, the course of the disease is slow and the total white-cell count is comparatively low. The disease may be properly diagnosed when, under these conditions, bone-marrow biopsy fails to reveal the pathologic changes characteristic of leukemia and splenic puncture shows the presence of megakaryocytes and immature cells of both the red-cell and white-cell series. Should the peripheral blood be suggestive and the bone marrow prove to be nonleukemic, splenic puncture is necessary in order to rule out those conditions in which splenectomy might be indicated, if only as a last resort.

The nature of the condition appears at present entirely obscure. For one reason or another, the bone marrow seems unable to form and deliver the requisite number of blood cells, but in view of the fact that at the height of the disease or

at death the bone marrow may be on histological examination normal, fibrotic, fatty or hyperplastic, it is by no means certain that bone-marrow failure is the primary lesion. Vaughan[3] has suggested that the "leukoerythroblastic hyperplasia" and the marrow sclerosis are processes which occur simultaneously in response to a single stimulus. It is difficult to reconcile this hypothesis with the extremely varied marrow pictures,—which do not always include sclerosis,—and for the present we must rest content with the knowledge that massive extramedullary myelopoiesis may occur, and that more definite hematologic disorders may thereby be simulated.

Conclusions

A total of 10 cases of agnogenic myeloid metaplasia are presented (Table 1).

In all instances, the spleen showed marked myeloid metaplasia, namely scattered foci of immature red and white blood cells and megakaryocytes throughout a slightly or markedly fibrosed organ. In the cases that came to autopsy there were occasionally found similar foci of ectopic blood formation in the liver and lymph nodes. There was not the uniform distribution of immature cells seen in the organs of leukemic patients, and immature cells of the red-cell series were present in greater numbers than in that disease. The Malpighian corpuscles were for the most part uninvolved. The bone marrow was variously fibrotic, hyperplastic, aplastic or normal. In no instance was it even suggestive of leukemia.

In 3 cases the diagnosis of myeloid metaplasia seemed clearly established and treatment was symptomatic only. All three patients are alive. In 1, a diagnosis of hemolytic jaundice was made and splenectomy was performed. The patient died three days postoperatively.

In 2 cases no definite diagnosis was made, but splenectomy was advised and carried out. In neither case was there any improvement in the peripheral blood picture, and both patients died within a year.

In 4 cases a definite diagnosis of myelogenous leukemia was made. One patient was treated symptomatically and died three years from onset. The three others were given x-ray treatment. Two died within six weeks; in the third case no real benefit occurred and the patient succumbed to bronchopneumonia two years later.

Table 1.

Case No.	Age	Sex	Duration to date	Duration to death	Duration after treatment	Red-Blood-Cell Count	White-Blood-Cell Count	Treatment	Condition of Bone Marrow	Icteric Index	Reticulocytes
	yr.		yr.	yr.		$\times 10^6$	$\times 10^3$				%
1	63	F	—	6	3 days	0.8–2.1	27.0–25.0	Splenectomy	Hyperplastic	50–17	38–45
2	52	M	—	16	5 wk.*	3.4–1.0	23.0– 3.0	X-ray	Fibrotic	—	—
3	60	M	—	?15	6 wk.	4.8–1.7	13.0– 4.0	X-ray	Aplastic	—	0.1
4	51	F	?8 ?16	—	—	5.3–7.6–3.7	28.0–16.0	Symptomatic	Fibrotic	7	2.8
5	49	M	2	—	—	3.9–4.1	8.6– 5.0	Symptomatic	Fibrotic	10–6	3.2
6	30	F	—	21	1 yr.	3.1–5.0	7.0–53.0	Splenectomy	Normal	6	5
7	70	F	—	?3	—	2.0–0.92	18.9– 1.3	Symptomatic	Fibrotic	3	10
8	22	M	—	7	2 mo.	3.9–3.0	12.0–70.0	Splenectomy	—	9	1–2
9	64	F	—	5	3 yr.	3.8–2.5	11.0–36.0	X-ray	Osteosclerotic	—	1–7
10	52	M	22 mo.	—	—	7.5–4.5	14.0	Symptomatic	Fibrotic	3	3.1

*This patient had had a small amount of irradiation 4 years previously.

The average duration from onset to date of death was 10.8 years. In 4 cases the symptoms dated back over fifteen years.

The chief symptoms were weakness, abdominal distress and a hemorrhagic tendency.

The principal findings were a progressive enlargement of the spleen, a moderately elevated or slightly depressed white-cell count and the constant presence of immature red and white cells in the peripheral blood.

In view of the apparent uselessness and possible harm arising from irradiation or splenectomy, it is of the greatest importance to recognize this condition and to undertake only symptomatic and supportive treatment when it has been proved to be present.

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Abstracts of the Remaining Five Cases

Case 5 (No. 914,393). M. G., a 49-year-old man, was admitted on October 11, 1937, with the complaint that for 4 months he had noticed a painless lump in the left upper quadrant of the abdomen. There were no other symptoms.

On physical examination, the spleen was 14 cm. and the liver 8 cm. below the costal margin. The red-cell count was 3,980,000, the hemoglobin 70 per cent (Sahli) or 10.92 gm. per 100 cc., and the white-cell count 8600, with 18 per

cent polymorphonuclears, 22 per cent young polymorphonuclears, 5 per cent metamyelocytes, 21 per cent myelocytes, 3 per cent stem cells, 25 per cent lymphocytes and 6 per cent monocytes. The platelets were decreased in number, and in counting 100 white blood cells 8 nucleated red cells and 1 normoblast were seen. Both anisocytosis and poikilocytosis were marked. The hematocrit reading was 33.3 per cent, the mean corpuscular volume 83.6 cu. microns, the mean corpuscular hemoglobin concentration 33.8 per cent and the mean corpuscular hemoglobin 27.4 micro-microgm. The icteric index was 10. On two occasions the basal metabolic rate was +50 per cent.

A sternal bone-marrow biopsy (S-37-3415) showed extensive fibrosis. Very rare scattered myelocytes and megakaryocytes were found in the dense connective tissue. There was no evidence of red-cell formation. No specific therapy was given. A splenic puncture performed on November 10, 1938, showed a marked degree of myeloid metaplasia. To date the patient's condition has remained essentially the same.

CASE 6.* G. C., a 30-year-old woman, was first seen on March 21, 1934. Seventeen years previously a physician had found her spleen enlarged. She had remained in fairly good health until 1930, when she began to complain of increasing weakness and some bleeding from the gums. Physical examination in March, 1930, revealed a spleen which descended to the level of the umbilicus. The red-cell count was 3,190,000, the hemoglobin 60 per cent (Sahli) or 9.3 gm. per 100 cc., and the white-cell count 7000, with 65 per cent polymorphonuclears, 10 per cent young polymorphonuclears, 3 per cent myelocytes, 17 per cent lymphocytes, 2 per cent basophils and 3 per cent eosinophils.

Early in 1935 the patient began to suffer from attacks of right lower quadrant pain, and in June, 1936, the white-cell count had risen to 53,000, with 53 per cent polymorphonuclears, 17 per cent metamyelocytes, 3 per cent myelocytes, 6 per cent eosinophils, 1 per cent basophils and 20 per cent lymphocytes. The red-cell count was 4,100,000. The reticulocyte count was 5 per cent, and 6 nucleated red cells were seen in counting 100 white blood cells.

Early in 1937 a splenectomy was performed. The spleen (S-36-3890) weighed 1100 gm. and showed marked fibrosis and myeloid metaplasia. Following operation, there was no essential change in the patient's condition. She eventually developed a bacteremia and septicemia from which she died in the middle of 1938.

Autopsy (S-38-2553) revealed the usual picture of staphylococcal septicemia with multiple abscesses of the lungs. Microscopically the liver showed a slight increase in the periportal connective tissue. There were a moderate number of myelocytes in the portal areas and in the sinusoids. No nucleated red cells or evidence of red-cell formation was seen. Megakaryocytes were present in large numbers in the sinusoids. The bone marrow showed no fat tissue, but was filled with hematopoietic tissue. Although the marrow was highly cellular, it in no way suggested leukemia.

CASE 7 (No. 692,414). A. B., a 70-year-old woman, was admitted on December 7, 1932. In 1930 she had noticed increasing fatigability and anorexia. In 1931, the weakness increased and she became increasingly dyspneic on exertion. On physical examination in 1931 the mucous membranes were pale. The spleen was palpable 2 cm. below the costal margin. The red-cell count was 2,000,000, the hemoglobin 28 per cent (Sahli) or 4.37 gm. per 100 cc., and the white-cell count 18,900, with 46 per cent polymorphonuclears, 7 per cent myelocytes, 35 per cent lymphocytes, 8 per cent monocytes, 3 per cent basophils and 1 per cent eosinophils. The reticulocyte count was 10 per cent, and 10 nucleated red cells were seen on counting 100 white blood cells. A fragility test showed a trace of hemolysis at 0.56 and complete hemolysis at 0.30. The hematocrit reading was 15.6 per cent, the mean corpuscular volume 78 cu. microns, the mean corpuscular hemoglobin concentration 28 per cent, and the mean corpuscular hemoglobin 21.9 micro-microgm.

Throughout her short stay in the hospital, the patient ran an irregular temperature from 99 to 101°F. She failed rapidly, and on January 30, 1933, the red-cell count had fallen to 925,000, the hemoglobin to 13 per cent (Sahli) or 2.03 gm. per 100 cc., and the white-cell count to 1300. The differential count remained essentially the same. The patient died February 3, 1933.

Autopsy (A-33-109) revealed nothing of note grossly, with the exception of chronic cholecystitis with cholelithiasis. The spleen weighed 410 gm. Microscopically it showed a slight degree of diffuse fibrosis and marked myeloid metaplasia. The liver weighed 1340 gm. and grossly was not remarkable. A moderate number of stem cells occurred scattered and in clumps in the sinusoids. Several foci of immature red cells and fairly numerous megakaryocytes could be recognized also in the sinusoids. The vertebral bone marrow had patchy areas of fibrosis. Where the fibrosis was marked, only a few hematopoietic cells were present; elsewhere they were numerous. Of the granulocytic series, stem cells, myelocytes and adult granulocytes were numerous. The red-cell series was represented by clumps of stem cells and erythroblasts, occasional normoblasts and rare nucleated red cells. Megakaryocytes were numerous, many of them young. A considerable amount of hemosiderin was present, especially in the fibrotic areas. The sternal bone marrow showed a moderate amount of fibrosis.

CASE 8 (No. T-988). S. S., a 22-year-old medical student, noted during routine classwork in June, 1926, that his own blood smear was abnormal, in that the red cells showed considerable variation in size and shape and that myelocytes were present. In 1925, on routine physical examination, it had been noted that his spleen was easily palpable.

Physical examination in 1926 showed that the spleen was palpable 2 cm. below the left costal margin. Otherwise, the physical examination was normal. The red-cell count was 3,900,000, the hemoglobin 83 per cent (Sahli) or 12.95 gm. per 100 cc., the white-cell count 12,000, with many immature white blood cells. The reticulocytes were 1.5 per cent and the fragility was normal. The white-cell count rose steadily to 40,000, with many myelocytes. The red-cell count rose coincidentally to 4,500,000, and the hemoglobin to 100 per cent (Sahli) or 15.6 gm. per 100 cc.

For the next five years the patient was lost track of, but during this time the spleen gradually increased in size. He was admitted to the hospital on September 12, 1932. The physical examination was normal except that the spleen descended 12 cm. below the costal margin. The red-cell count was 4,500,000, the hemoglobin 80 per cent (Sahli) or 12.48 gm. per 100 cc., and the white-cell count 15,000, with 70 per cent polymorphonuclears, 5 per cent metamyelocytes, 1 per cent myelocytes, 1 per cent stem cells, 3 per cent monocytes and 20 per cent lymphocytes. The hematocrit reading was 42.2 per cent, the mean corpuscular volume 93.8 cu. microns, the mean corpuscular hemoglobin 27.7 micro-microgm. and the mean corpuscular hemoglobin concentration 29.6 per cent. A fragility test showed that

*For the report of this case, we are indebted to Dr. Arthur W. Marsh of Worcester, Massachusetts.

hemolysis began at 0.56 and was complete at 0.30. The icteric index was 9.

On October 28 splenectomy was performed. The spleen weighed 745 gm. Microscopically there were focal collections of stem cells and myelocytes. Numerous foci of red-cell formation were present. The number of megakaryocytes was considerable. The Malpighian corpuscles were well preserved. Lymphocytes and plasma cells were scattered through the pulp.

The patient's condition remained good, but the red-cell count fell to 3,000,000 and the white-cell count rose to 70,000 on November 20, with 80 per cent polymorphonuclears, 7 per cent metamyelocytes, 3 per cent myelocytes and 10 per cent lymphocytes. The platelets were normal. An occasional nucleated red cell was seen. The patient's strength gradually failed and he died of bronchopneumonia on January 11, 1933. No autopsy was obtained. It is unfortunate that in this case bone-marrow biopsy was unsatisfactory.

Case 9 (No. 824,534). D. W., a 64-year-old woman, was admitted to the hospital on July 2, 1931, complaining of weakness of 4 months' duration. Two years previously she had had a severe attack of weakness, and at this time it had been noted that the spleen was enlarged.

Physical examination was essentially normal, except for a spleen which extended 7 cm. below the costal margin. The red-cell count was 3,830,000, the hemoglobin 71 per cent (Sahli) or 11.08 gm. per 100 cc., and the white-cell count 11,900, with 1.7 per cent reticulocytes. No record of a differential count was made, but it was noted that many immature granulocytes were present. There was no free hydrochloric acid in the gastric juice. A diagnosis of myelogenous leukemia was made and the patient was put on Fowler's solution by mouth. She left the hospital, however, and was not seen again until January 31, 1935, when she was readmitted for increasing weakness and nervousness.

Physical examination at that time revealed a hard, nontender spleen extending to the level of the umbilicus. Otherwise the physical examination was normal. The red-cell count was 3,060,000 and the hemoglobin 57 per cent (Sahli) or 8.89 gm. per 100 cc. The white-cell count was 17,000, with 65 per cent polymorphonuclears, 2 per cent metamyelocytes, 17 per cent myelocytes, 12 per cent lymphocytes, 1 per cent eosinophils and 2 per cent basophils.

The patient was given 400 r to the spleen. Five weeks later the white-cell count had risen to 40,000.

She was readmitted on March 5, 1934. At this time the spleen had increased still further in size, now reaching to the iliac crest, and the liver was 5 cm. below the costal margin. The red-cell count was 3,940,000, the hemoglobin 68 per cent (Sahli) or 10.61 gm. per 100 cc., and the white-cell count 28,600, with 13 per cent polymorphonuclears, 41 per cent young polymorphonuclears, 6 per cent myelocytes, 6 per cent premyelocytes, 5 per cent stem cells, 4 per cent basomyelocytes, 4 per cent basophils, 1 per cent monocytes and 11 per cent lymphocytes.

The final admission was on May 28, 1936. The patient had lost much weight and was somewhat dyspneic. There were signs of bronchopneumonia at the bases of both lungs. The liver and spleen were as before. The temperature was 100.4°F., the pulse 100 and the respirations 30.

The red-cell count was 2,500,000, the hemoglobin 43 per cent (Sahli) or 6.71 gm. per 100 cc., and the white-cell count 36,000, with 25 per cent polymorphonuclears, 12 per cent lymphocytes, 10 per cent monocytes, 48 per cent myelocytes, 2 per cent basophilic myelocytes and 3 per cent stem cells. The patient died the day of entrance.

Autopsy (A-36-311) showed lobar pneumonia, splenomegaly, hepatomegaly with hemosiderosis, cholelithiasis and osteosclerosis of the vertebral and sternal marrows. The spleen weighed 1570 gm. The liver weighed 2480 gm. The lumbar and sternal marrows were pinkish gray and hard. The tibial and femoral marrows were yellowish white. Microscopically the spleen showed a moderate degree of diffuse fibrosis. Many focal collections of stem cells, myelocytes and adult granulocytes were present. There was no evidence of red-cell formation, nor were any immature forms of this series noted. Megakaryocytes were numerous. The Malpighian corpuscles were smaller than normal, and many contained a few stem cells and megakaryocytes. Hemosiderin-filled macrophages were present in large numbers in the pulp. The sinusoids of the liver contained numerous stem cells, immature granulocytes and a considerable number of megakaryocytes. No evidence of red-cell formation was present, nor were any immature red cells seen. Large amounts of hemosiderin occurred in the liver cells, the Kupffer cells, and in macrophages in the portal areas. The tracheobronchial lymph nodes contained some myelocytes and polymorphonuclear leukocytes and also some megakaryocytes, but no immature red cells. There was much hemosiderin in the stromal fibroblasts and the endothelial cells of the sinuses. The sternal bone marrow showed an increased number of bony trabeculae and areas of connective tissue. Large numbers of fat cells were present. There were foci of the granulocytic series with normal maturation. No evidence of red-cell formation was present. Megakaryocytes were fairly numerous. Large amounts of hemosiderin were present. The vertebral and rib marrows presented essentially the same picture. The femoral and tibial marrows contained much fat tissue and a few myelocytes, polymorphonuclear leukocytes, lymphocytes and macrophages.

Case 10 (H. 39. 1280). L. B., a 52-year-old man, was admitted to the hospital on October 16, 1939, with a chief complaint of abdominal distress. His past and family histories were irrelevant, except that in recent years he had suffered a good deal from "rheumatism" of the knees and ankles. In February, 1938, he noticed that he was losing weight and that he tired easily. Three months later he began to have dyspnea on exertion. At about the same time he noted vague abdominal distress. His abdomen gradually became distended and in July, 1939, he noted a hard, nontender mass in the left upper quadrant. At this time he visited an outside hospital, where the red-cell count was found to be 7,590,000, the hemoglobin 90 per cent (Sahli) or 14.0 gm. per 100 cc., and the white-cell count 14,750. The differential count was essentially normal. The spleen at that time was grossly enlarged, extending to the midline and to the iliac crest. Otherwise the physical examination was normal.

On entry to the hospital in October, 1939, physical examination disclosed a hard, smooth spleen extending to the right of the midline and into the false pelvis. The liver was palpable 3 cm. beneath the costal margin. There was evidence of considerable recent weight loss. The red-cell count was 4,800,000 and the white-cell count 14,500, with 37 per cent polymorphonuclear neutrophils, 9 per cent young polymorphonuclears, 4 per cent metamyelocytes, 13 per cent myelocytes, 3 per cent stem cells, 13 per cent monocytes, 10 per cent lymphocytes, 3 per cent basophils, 1 per cent eosinophils and 7 per cent of abnormal cells closely resembling megakaryocytes. A rare normoblast was

seen. Two weeks later the hematocrit reading was 29 per cent, the mean corpuscular volume 61 cu. microns, the mean corpuscular hemoglobin concentration 34 per cent and the mean corpuscular hemoglobin 23.7 micro-microgm. The red-cell diameter was 6.04 microns. Fragility tests showed that there was a moderate increase of the red cells to hemolysis, which began at 0.52 and was complete at 0.32.

A biopsy (S-39-3327) of the sternal marrow showed very extensive fibrosis, but here and there were scattered cells of the hematopoietic series. The marrow (S-39-3432) from the mid-tibia was largely fatty, but here and there areas of fibrosis occurred, containing small collections of immature blood cells of all types. Young blood cells were not seen in the fatty areas. A specimen (S-39-3422) removed at splenic puncture showed marked fibrosis, large numbers of megakaryocytes and many nucleated red cells, normoblasts, myelocytes and stem cells. A definite diagnosis of agnogenic myeloid metaplasia was made.

PENTOTHAL SODIUM ANESTHESIA FOR ENCEPHALOGRAPHY*

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ENCEPHALOGRAPHY, when first described by Dandy[1] (1919), was intended as an aid in the diagnosis of hydrocephalus and brain tumor. The introduction of air through the lumbar route was little utilized until 1921, when it was reintroduced and its importance emphasized by Bingel and Wideroe.[2] Since then its use has been extended to the investigation of practically every disease within the cranial cavity, and it has become an indispensable adjunct to neurological diagnosis.

Encephalography can be one of the most drastic diagnostic procedures patients have to undergo; serious symptoms and occasionally death can occur, and in fact have occurred, during this procedure and after its completion. When encephalography is done under local anesthesia after preliminary sedation "the usual symptoms in the order of their appearance are: headache, nausea, vomiting, pallor, perspiration, chilliness, drowsiness, restlessness, poor pulse."[3] We have adopted the use of Pentothal Sodium intravenously to produce anesthesia in patients subjected to encephalography in an attempt to avoid these immediate reactions. Some clinics have used the general anesthetics, ether and ethyl chloride, for the same purpose. Solomon and Epstein[4] (1932) recommended the use of nonvolatile anesthetics, pentobarbital, Amytal or Avertin, and reported good results with the intravenous injection of 0.3 to 0.5 gm. of pentobarbital-sodium.

In our series of 266 encephalograms from 1935 to 1938 inclusive, Pentothal Sodium (sodium ethyl-l-methylbutylthiobarbiturate) was used as an intravenous anesthetic in 177 cases and Evipal Soluble (sodium salt of N-methylcyclo-hexenyl-methyl-barbituric acid) in 5. Of the remaining 84 cases, which represent a transition period in 1935 and the early part of 1936, before intravenous anesthesia had been fully accepted as a method of choice, encephalography was done in 28 cases under local infiltration anesthesia, in 11 under Avertin plus local infiltration, in 30 under Avertin, in 6 under Avertin and Vinyl Ether, in 4 under Vinyl Ether and in 5 under open ether. There has been no death in this series.

With Pentothal Sodium intravenous anesthesia, the one-hour to two-hour period of postencephalographic somnolence is very helpful to the patient, as it is during this period that the headaches ordinarily are most severe. On reviewing the records of those patients who had intravenous Pentothal Sodium anesthesia and subarachnoid oxygen insufflation, we found that the average duration of the postencephalographic headache was twenty-four hours. A few of the patients had no headache, while others complained of it for two to three days and, rarely, some had it for five days. Nausea and vomiting when they occurred after encephalography were confined to the first six or eight hours.

DOSAGE

The only reliable guide to dosage is the physiologic response of the individual patient. Our experience has shown that the earlier notion of predetermining dosage from body weight may be dangerous. The very old, debilitated patient requires less, while the young, robust, healthy, muscular individual requires more. Patients who have formerly taken daily doses of the barbiturates, such as luminal, for control of convulsions seem to require more because of a tolerance they have acquired for this group of drugs. The average dose of Pentothal Sodium in our series was

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0.85 gm., and this provided anesthesia for the introduction of air and taking of roentgenograms, which together took thirty or thirty-five minutes. The minimum dose was 0.3 gm., and the maximum 2.0 gm.

Premedication

In most cases atropine sulfate, 1/150 gr., was administered subcutaneously one hour before operation, as this medication decreased the formation of mucus and seemed to decrease the frequncy of laryngeal and bronchiolar spasm. A few of the patients received morphine sulfate, 1/6 gr., and atropine sulfate, 1/150 gr., subcutaneously and pentobarbital-sodium, 1½ gr., orally one hour before operation, but there was no apparent advantage from this combination of premedicants.

Administration

Close adherence to a definite precautionary routine before the anesthesia is started will prove valuable: one should test intravenous apparatus to be sure it functions properly, obtain the necessary saline solution from a sterile labeled bottle or flask, have airways within reach of the anesthetist and, most important of all, have a gas machine at hand so that in case of emergency oxygen may be administered under pressure.

The patient is seated near one end of the x-ray table with his legs hanging over the side and his head resting on the shoulder of an assistant so that his face is toward the anesthetist, as shown in Figure 1.[5] This is important, as the anesthetist can more readily observe respiration and color, and insert airways or administer oxygen if the patient's face is toward him. Usually the median basilic or the median cephalic vein in the left antecubital space is selected for the site of injection. The solution strength now used is 5 per cent in saline; the 10 per cent solution originally employed was discontinued because it occasionally caused slough or local reaction when accidentally injected into the tissues outside the vein.

The 5 per cent solution is aspirated into a 20-cc. syringe, preferably with an eccentric tip, to which is attached a needle of the anesthetist's preference. One of us (L. F. S.) has employed to advantage a piece of rubber tubing to connect the syringe and needle in giving intravenous agents. The rubber tubing is approximately 30 cm. long, of fairly small bore and thick-walled, with a stopcock and glass adapter at one end for the needle, and at the other end a metal adapter into which the syringe tip fits. The syringe is filled with the solution, the tubing connected, a needle attached to the glass adapter and the stopcock turned off. After proper preparation of the selected area, the tourniquet is applied to the arm, venepuncture made and the stopcock opened. As soon as the blood appears in the glass adapter the tourniquet is released and the needle strapped into place with adhesive; the syringe may also be strapped to the patient's arm or simply held by the anesthetist. This flexible connection between the syringe and needle has helped to prevent the needle from being pushed through the posterior wall of the vein, as so often occurred with the syringe and needle rigidly connected, when the patient was placed on the table for taking roentgenograms.

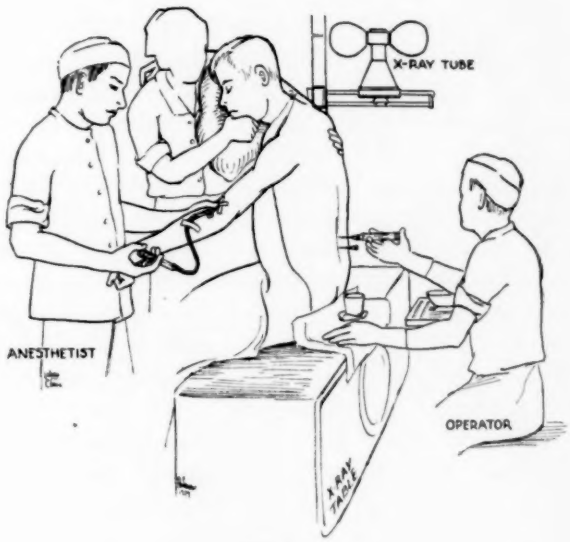

Figure 1.

Routine use of either a nasal or oral airway is preferred by some, while others use them only when respiratory obstruction is observed. A cotton wisp fastened to the patient's upper lip may be used as an aid in determining the character of respiration,[6] or the anesthetist may listen to the respiratory exchange for any obstruction that may occur.

Injection of the Pentothal Sodium solution is started by the fractional method, and the patient is instructed to count aloud. Initially 3 to 4 cc. is slowly injected in approximately fifteen seconds, and after a brief pause to give the solution time to circulate in the blood stream, and permit any individual idiosyncrasy to become manifest before a potentially toxic dose has been administered, another small injection is made. With very young, or aged and debilitated patients the initial injection should be smaller in amount and the rate of

administration undertaken slowly and cautiously, always observing the patient's respiration.

These small, carefully administered injections are continued until impairment of speech, depressed respirations, loss of conjunctival reflexes and gradual relaxation of the patient mark the onset of anesthesia. Respirations are normal during light anesthesia and become increasingly shallow as anesthesia deepens. While the spinal puncture is being made the patient usually requires an additional small dose of the solution to overcome the painful stimulation.

With the use of the slow, intermittent injections separated by safety pauses, and the maintenance of a clear airway, little difficulty from the anesthetic can be expected. Rarely hiccups will be disturbing, but they can usually be controlled by increasing the depth of anesthesia. On a few occasions patients have shown respiratory depression and anoxemia, which we attribute to overdosage due to too rapid injection. This emergency is handled by oxygen inhalation under pressure or artificial respiration. Respiration can occasionally be started when the patient is still in the sitting position by gentle intermittent pressure over the short ribs.

After the spinal fluid has been replaced by the injected gas the patient is placed in the supine position on the x-ray table and the anteroposterior roentgenograms are taken. Before turning the patient over for the posteroanterior and lateral stereoroentgenograms a final small injection is made; this will generally keep the patient quiet for remaining roentgenograms.

Advantages, Disadvantages and Contraindications

The advantages of intravenous Pentothal Sodium anesthesia are as follows: It provides the neurosurgeon with adequate anesthesia for lumbar puncture, air injection and roentgenography, as the patient is quiet and in good condition throughout the procedure; it overcomes the undesirable reactions formerly seen when encephalography was done under local anesthesia — headaches, nausea, vomiting, pallor, cyanosis, perspiration, chilliness, restlessness and poor pulse; it eliminates the danger of fire or explosion present when inflammable agents such as ether or ethyl chloride are used in the x-ray room[7]; it provides rapid, smooth and pleasant induction for anesthetizing patients in the sitting position; and it eliminates the possibility of psychic shock.

The disadvantages are these: There may be difficulty in making the injection in certain obese individuals whose veins are small and deeply situated; there is possibility of local reaction if large amounts of the solution are injected in the tissues outside the vein.

Pentothal Sodium anesthesia, given intravenously, is contraindicated in children under seven or eight years of age, since venepuncture is sometimes difficult and maintenance of an even plane of anesthesia is almost impossible, because the patients pass so quickly and unpredictably from one stage of anesthesia to another with the administration of small amounts of the drug; in hepatic insufficiency, jaundice and severe renal disease, as detoxication and urinary elimination are impaired; in patients with increased intracranial pressure with possible medullary compression, because the respiratory center is already embarrassed and the addition of more respiratory depression by Pentothal Sodium may prove fatal; and in patients receiving treatment with sulfanilamide. As the work of Adriani[8] suggests, this combination of sulfanilamide and barbiturate may be unwise.

Summary

The development of the barbiturates that are both transient and effective in their action has given us a satisfactory intravenous anesthesia for encephalography. A series of cases is briefly presented, giving a method of administering Pentothal Sodium for intravenous anesthesia during encephalography, and the management of complications that may occur. The advantages of this type of anesthesia and its disadvantages and contraindications are also presented.

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NURSING, NURSES AND DOCTORS*

STEPHEN RUSHMORE, M.D.

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IN NURSING there are many serious problems: of caring for the sick, of education, of administration, of adjustment to a rapidly changing order so perplexing that one must face the question of what it is that changes and what it is, if anything, that does not change. In working out the solution of these problems the spirit of controversy is to be avoided as contributing little illumination, and it is necessary to have wisdom, which includes vision and imagination, insight and creative capacity, endurance and patience. This means, when one has a vision of a goal, of one's ideal, that there shall be no undue haste in seeking its realization. Short cuts are sometimes useful but often dangerous, and it is a false doctrine that the goal can be reached without paying attention to the path taken in pursuing it. The way a thing is done will often determine which one of several possible goals is to be attained.

In entering upon a field of controversy, only the scientific spirit can be relied upon as a guide. This means not merely a willingness or even a desire to consider the facts, but a determination to consider all the facts in the case. In one of his essays, William James, with great insight and a keen sense of humor, refers to the "fluidity of the facts," by which he means, as can be judged by what he said elsewhere about "stubborn and irreducible facts," that it is opinions about facts that have this fluidity. It is very difficult to look at all the facts at one time, difficult physically and mentally, because really only one thing at a time can be seen. However quickly the eyes are shifted, at the risk of strabismus, attention to one thing means lack of attention to something else which may also be of vital importance. Thus it is very difficult to see things in proper perspective, difficult but necessary.

As one looks over the whole field of the healing art and sees the multitude of efforts that must be put forth by many kinds of persons, by many groups of individuals, two groups stand out as different from all the others because they come into direct contact with the sick, namely the physician, who has the prime responsibility, and the nurse, who has the secondary responsibility.

Here are all the persons directly involved in the care of a case of serious illness: the patient, the doctor, the nurse. The hospital superintendent administers merely so that the doctor and the nurse can do their work under better conditions; the medical school is for the education of the doctor, the nursing school for the education of the nurse; the laboratory workers, the technicians, the pharmacists, all help the doctor so that he can help the patient. It is this direct care of the patient that marks off the work of the nurse as different from that of all the other assistants to the physician.

Nursing may be regarded from another point of view. What are the things to be done in nursing? Into what parts can the whole field be divided? There are multitudinous needs which do not require enumeration now, but a practical question is: How many kinds of nurses are required to meet these needs? One answer is, as many kinds of nurses as there are needs. These speculations suggest remoteness from the solid earth of actual practice, for one nurse may perform many kinds of service, meeting thereby as many needs, and a pertinent question is: What is this discussion of kinds of nurses about anyhow?

The full answer would take too long a time to be given now, but a partial answer is given by the dollars and cents involved, by practical economics. In general, people are going to buy such nursing service as they think they need. If they need only a little nursing skill and that is available, they will buy it; if they need much and can get it, they will buy that. But if a little will fill their need, they are not going to pay for something they do not need and cannot use.

On the basis of need of the patient, several levels of nursing service are demanded and will be supplied, and if some classification of nurses is thought desirable, there are two groups, the more highly skilled and the less highly skilled. But such distinction is rather arbitrary as a basis for classification and presents no clear-cut differentiation. In the actual practice of nursing, the nurse does what the doctor directs her to do, according to his idea of the skill of the individual, and not according to her classification.

There is a further question as to how much work there is to be done by these two groups respectively, and the kind of work and the conditions under which it is to be done. Broadly speak-

*An address given at the graduating exercises of the School for Attendant Nurses, Household Nursing Association, Boston, November 23, 1939.

ing, the more highly skilled worker is in the general hospital dealing with acute illness, and the less highly skilled worker is out of the general hospital and deals with chronic illness, or acute illness when the convalescence has begun. There are, to be sure, acute cases at home and chronic cases in hospitals, very many of them, but in a general way the distinction which has been made is sound. It is probably true that the field for the less highly skilled worker is larger and the opportunities, in this sense, are greater, but they are less dramatic and less spectacular.

No use here has yet been made of a specific designation for either of the two kinds of workers in order that any possible prejudice from terms already employed might be avoided, for it is basic facts rather than superficial designations that are important. The basic fact is that one group is more highly trained and the other group is less highly trained, and if one is called the nurse and the other the attendant, there can be no serious objection. Both are in substance and in practical activity workers in the field of nursing by direct ministration to the needs of sick persons: both are actually nurses.

Reference has been made to the problems connected with these two groups of workers as of similar magnitude in the sense of the number of persons needing the service and the number of persons needed to render the service. This introduces another problem, namely, the need, in a field so extensive and so important for the well-being of the public that there should be some control by the state of all persons who offer themselves for this service. Protection is needed against incompetence, whether due to lack of knowledge or lack of skill or lack of moral stamina. Should not every worker in the field of nursing be licensed by the state as qualified to undertake such duties and responsibilities?

An immediate and natural answer to this question is: "Yes; of course they should all be licensed. It is terrifying to think of the harm that might be done by incompetent nurses." This answer has been given by some persons who, however sincere and earnest and unselfish, have not, it appears, thought out to all the practical details the implications of what they propose to do. Some of these details will be noted later.

The next very practical question is: How shall each group be prepared for their work; how shall they be trained; or, better, how shall they be educated? The word "education" in this connection needs no justification, for if this experience in the school of nursing is looked upon as mere training, there is failure to recognize that the candidates are human beings, preparing themselves for what may be their lifework.

It is clear that considerable time and effort have been directed, in the past twenty-five years, to determining how the more highly skilled worker should be educated, and while the system is by no means perfect, a good, workable and fairly adequate scheme has been devised. But it is a matter for surprise and deep concern that so little attention has been given to the education of the less highly skilled worker. This education of the attendant is in the very early stage of an experiment, and while the school which is carried on by the Household Nursing Association represents a fine piece of work, it has not received in Massachusetts or in other states the enthusiastic imitation that the project deserves. It is a fact that while there has been some talk in the past twenty-five years among persons interested in nursing education, there has been very little done for the attendant; and in some quarters there has been of late an unwillingness even to talk about these problems.

It is because there is no generally accepted body of ideas about education of attendants, incarnate in effective institutions, that the highly experimental stage should be continued for some time longer, until there can be crystallized a reasonable procedure, with a sound experimental basis. What is required now is freedom to experiment, and during the period of experimentation, it may be wise for the state to assist by licensing, on the basis of certain qualifications, persons who desire legal recognition. Licensing gives the attendant the recognition and the status that are appropriate, but until this experiment is distinctly farther along in its development, it would be a serious mistake to have compulsory registration of all who render nursing service. Of prime importance in the working out of a problem as complicated as this, and one which has so many aspects which need consideration, is patience. It is folly to secure legislation of which the consequences have not been thought through and realized clearly. Freedom to experiment in educational procedures is necessary for progress, yet it may be lost with the introduction of such compulsory requirements as have appeared in some drafts of proposed legislation.

The argument for compulsory registration is the protection of the public. But if one listens to the accounts of possible suffering from incompe-

tent nursing as set forth by advocates of compulsory registration, and compares those accounts with what one actually finds, one may well be distressed; yet the actuality does not seem to be so bad as it is represented, and nothing is said of incompetence among registered nurses. Why is the situation not so bad as some persons say it should be without compulsory registration? Very briefly, it is because the chief responsibility for the care of the sick is on the physicians, and it is they who have the responsibility for poor nursing and for good nursing. If they insist on good nursing for their patients, they can usually get it. If they are satisfied with poor nursing, the patients suffer. Nurses do not realize with sufficient clearness that nursing can never rise above the level of medicine, and that to the medical profession they owe much, but not all, of what they have been able to accomplish.

What is the proper relation of the attendant to the nurse and of the nurse to the attendant? This cannot be gone into in detail, but one of the basic facts is that both justify their existence by the adequacy with which they render nursing service to sick persons. Both are rendering necessary services for which there will be a permanent need in society. In the final analysis, the relations will be determined by the reciprocal respect, on the part of each group, for what the other group is doing.

There is another problem which involves basic issues. If it is not solved properly the system that it supports breaks down. What is the relation of the nurse to the doctor? Some of the things that the nurse may do are part of the practice of medicine. This is true whether she is or is not registered. But she is permitted to do them because she is caring for the sick under the direction and supervision of the physician. If she gives nursing care to a sick person, not in emergency and not under the implicit or explicit direction of a physician, she is acting improperly. Now, the basic relation between doctor and nurse has unavoidable implications which some persons are not willing to acknowledge. The implications are not only a responsibility of the physician for what the nurse does in practice, to which reference has been made, but also a responsibility for participating in the education of the nurse and a responsibility for participating in the determination of her qualifications for the practice of nursing. It is true that some physicians are not willing to accept these offices, but that does not lessen the duty of the medical profession. Neither does it justify the claim that nurses alone should control the education of nurses, or that nurses alone should carry the responsibility for determining the qualifications of the nurse, who is to work only under the direction of the physician. In the field of the healing art, the nurse, whether registered or unregistered, is a subsidiary worker, and it is not likely that this relation will change in this generation. It is the part of wisdom to recognize this fact, and to make plans accordingly.

The final question concerns the status of nursing. Is it a profession? What is a profession? It was formerly easy to answer this question: there were three professions, theology, law and medicine. Now there are many others, and what a change has taken place in medicine itself! It was at one time deemed beneath the dignity of the physician to work with his hands, so the hand-worker or chirurgeon, from which comes the word surgeon, was a barber-surgeon. In the Oath of Hippocrates are these words: "I will not cut persons laboring under the stone, but will leave this to be done by men who are practitioners of this work." Just as medicine has grown to include surgery and has raised it to a professional level, so many callings once thought lowly have taken on a professional tinge. Even business, which had its origin in barter, a word which has apparently the same origin as barratry, a form of cheating, some would raise to the professional level.

The essential distinction of the profession is the spirit in which the worker does his work. The work of the nurse is, in part at least, ministering directly to the needs of sick and suffering human beings, and if they believe in the dignity and worth of humanity, even if they do not see very clearly what it is that gives that worth, and if, working for the benefit of their patients, they respect the patients and themselves, they will be able to live their own lives in the spirit of a profession.

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REPORT ON MEDICAL PROGRESS

HEMATOLOGY*

WILLIAM DAMESHEK, M.D.†

BOSTON

DURING the year 1939, most of the hematological advance centered on physiological rather than morphological principles. Whereas until recent years there was danger that preoccupation with morphology might result in a "dead" subject, there has recently been evidenced, at least in some quarters, a complete turnabout from morphology. The latter nevertheless has its place and its study need not be neglected, even though "dynamic" hematology has proved its preeminence.

During 1939, much was learned about hematological methods in diagnosis, motion-picture differentiation of the lymphoblast from the myeloblast, hematologic reactions to drugs, the experimental production of pernicious-anemia-like disease in animals, the gastric mucosa in pernicious anemia, the various events in iron metabolism, the pathogenesis of the hemolytic anemias, the treatment of polycythemia, and vitamin K and prothrombin.

BONE-MARROW BIOPSY

Although a number of observers regard biopsy of marrow by sternal puncture as practically a routine measure in the careful study of a hematologic case, there are others who maintain either that the procedure has no value or that its value is limited. As with many of the diagnostic developments in medicine, it is likely that widespread knowledge of the need for sternal puncture will become manifest only with the passing of time. One is thoroughly accustomed nowadays in the working out of a hematological problem to do a "complete" blood, whereas not so many years ago only a hemoglobin determination was thought essential. The hematocrit reading and the various indices, such as the mean corpuscular volume and the mean cell diameter, have all come to the forefront in recent years, and have proved of great value chiefly in appreciation of the pathologic physiology of a given hematological problem. Biopsy of the marrow by means of the sternal puncture is only slightly more difficult than venepuncture, and it gives much information regarding abnormal physiology. Regardless of possible diagnostic aid, its educational value alone in making the physician think in terms of bone-marrow disease is great. Too often, the blood is considered as a fixed sort of fluid containing certain types of cells. In reality, it is simply a circulating "roadway" with cells coming from the blood-forming organs on their way to certain tissues. At a given moment, the circulating blood may improperly reflect conditions in the marrow, the chief blood-forming organ, for a number of different conditions may present an identical blood picture. This is particularly true when pancytopenia is present — that is, a reduction in all the cells of the blood. Pancytopenia may be due to aplasia of the marrow, leukemic hyperplasia, Gaucher's disease, metastatic cancer, particularly of the sarcoma variety, severe infectious states, "spleen-liver" syndromes and certain deficiency states. Many of the diagnostic puzzles in hematology present pancytopenia; the remainder of the cases have, without too much attention to diagnosis, responded to the administration of liver extract, iron or both. It is therefore in the cases with anemia, leukopenia and thrombocytopenia that the sternal puncture is clearly indicated and is often of considerable diagnostic aid.

The technic of sternal puncture is simple, requiring novocainization of a small area in the midsternum in the region of the fourth interspace, and the insertion of an abbreviated lumbar puncture needle or a special sternal puncture needle‡ until a sensation of "give" is felt. In elderly people, the needle is readily inserted through the bony structure of the anterior lamella; in the young and middle-aged a certain amount of controlled pressure is required. Vogel and Bassen[1] recommend a 12-mm. 18-gauge needle for children over one year of age and a 6-mm. 20-gauge needle for infants under one year. They use no anesthesia. A small amount of marrow, never more than 1 cc., is aspirated with a 5-cc. or 10-cc. dry syringe. Inspection of the material in gross

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as it is aspirated and placed on slides often gives some idea as to the degree of hyperplasia, hypoplasia or leukemic infiltration. Smears are made on slides and stained either with Wright's stain, or with Giemsa's. With this method beautiful preparations usually are obtained, by means of which careful studies of the various types of nucleated red cells, white cells and megakaryocytes may be made. Sections may also be prepared by collecting some of the marrow material on filter paper, placing it in Zenker or Zenker-formol fixative and later staining it with eosin and methylene blue. Careful and long-continued practice with bone-marrow preparations should familiarize the observer with the various normal and abnormal cells and their relations to each other. The trephine method of biopsy which I formerly advocated is now used only if the puncture preparations are inadequate, or if definite confirmation is required regarding such abnormalities as Gaucher's disease, lymphoma, leukemic proliferation, aplasia of the marrow or osteosclerosis. In these conditions, the sternal puncture alone may be misleading or offer no diagnostic aid. An excellent and critical review of the subject of bone-marrow biopsy is that of Scott.[2]

Red Blood Cells

Paternity Tests

The use of blood groups in bastardy cases when the question of paternity is involved is receiving increasing attention. In the states of New York, New Jersey and Wisconsin the use of blood group tests in these cases is mandatory; if an individual refuses, he may be suspected of fraud. The tests can be used only to exclude paternity. By using the four ordinary blood groups (O, A, B and AB), paternity can be excluded in only about one sixth of the cases tested when child, mother and putative father are examined. By utilizing anti-M and anti-N testing serums (Landsteiner-Levine), it is possible to divide all individuals into M, N or MN groups. The use of both the ordinary blood groups and of the M and N factors leads to the exclusion of paternity in 33 to 40 per cent of the cases tested. Provided the serums are correctly prepared and the testing properly done and carefully checked, the results obtained are of definite and absolute value. The subject of blood grouping in the establishment of nonpaternity and in baby mixups has been covered by Wiener,[3] Levine[4] and Davidsohn and Rosenfeld.[5]

The Sedimentation Rate

In tubes in which blood has been prevented from clotting by an anticoagulant, the red cells sediment at a rate dependent to a great extent on certain changes in the serum. Some serums, notably those from patients with infectious diseases or any condition in which there is increased breakdown of tissue, have increased rates; that is, they have the property of causing red cells to sink rapidly. This very rapid settling is due to the formation of large aggregations of rouleaux. When rouleaux formation is for some reason impaired, as in sickle-cell anemia (Bunting[6]), the sedimentation rate is considerably slowed. Cutler, Park and Herr[7] point out that the effect of serum changes on the sedimentation rate is more important than that of anemia. These authors question the necessity of correcting for anemia. According to Ham and Curtis,[8] who have made a comprehensive review of the entire problem, the Rourke and Ernstene method is the most accurate. With this method, heparin is used as an anticoagulant, the rate of sedimentation is observed at five-minute intervals to obtain the second or true sedimentation phase and a correction for anemia by means of the hematocrit is made. Hambleton and Christianson,[9] on the other hand, state:

> Alleged improvements upon the Westergren sedimentation method have been presented which appear theoretically correct, *e.g.* correction for cell volume, the use of heparin in place of citrate and graphic methods of recording the results. Instead of making the test more valuable, these changes have the reverse effect, either by leading to results of less clinical value, or by making the test more tedious to perform or less clear to interpret without increasing its clinical value. Hence it is recommended that the Westergren method, by reason of its simplicity, reliability and priority, should be adopted as the standard method of performing the sedimentation test.

The sedimentation rate is so nonspecific that one questions the desirability of attempting too great accuracy with the procedure. Furthermore, it is important to realize that the test is by no means infallible: abnormal rates may be obtained in normal individuals, especially in the older age groups, and normal rates are often present even when serious organic disease, such as cancer, is present. The sedimentation rate should be regarded as a single laboratory procedure which, with all the rest of the data, may be of some significance in helping to evaluate a given problem. In the follow-up of such conditions as rheumatic fever, rheumatic heart disease, rheumatoid arthritis and coronary thrombosis the test is apparently

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of definite value. As with many other laboratory procedures, its value depends to the greatest extent on the observer's critical judgment.

Stiles[10] conducted an interesting comparative study of the value of blood smears and sedimentation rates in "low-grade chronic illness," such as nasal congestion, postnasal discharge, chronic bronchitis, colitis, prostatitis and rheumatic pains. The immature polymorphonuclear cells ("nonfilament cells") were increased in practically all these cases and their number returned to normal as the condition improved. More than 80 per cent of the sedimentation rates were abnormal. The blood smear, although a more sensitive indicator of the presence of disease, was found less significant because of this sensitivity. In infectious mononucleosis, even with marked disease present, the sedimentation rate is usually normal.

Stippling of the Red Cells

The clinical significance of punctate basophilia or stippling was studied by Falconer.[11] The Jenner-Giemsa stain was used and five thousand erythrocytes were studied in each case. In normal individuals, the "mean punctate basophilia" was 92 per million red cells. In various types of anemia not due to lead, the counts varied from 2000 to 27,000. In 8 workers exposed to lead but free of symptoms, the average stippled count was 2100 per million red cells. Thus stippling, although common in lead poisoning and often diagnostic, is not pathognomonic of the condition, but may occur in various states, particularly when associated with anemia. Absolute diagnoses in questionable cases are made by urinary-excretion studies, spectrographic determinations of the blood and urine and so forth.

Indices

The various devices for estimating the dimensions of the normal and abnormal red cell are by now well known, and are coming into increasingly common usage. These have been popularized by Wintrobe and include mean cell diameter, mean cell volume, mean cell thickness, mean corpuscular hemoglobin concentration and so forth. Of these, the mean corpuscular volume has come into the widest use, superseding to a great extent the more laborious methods of Price-Jones for differentiation of normocytic, macrocytic and microcytic anemias. There is at times, however, an unfortunate tendency to diagnose macrocytic anemia when the mean corpuscular volume is only slightly elevated above the normal range of 84 to 94 cubic microns. In severe anemia, when slight fluctuations in hematocrits and erythrocyte counts may result in marked changes in the estimated mean cell volume,* a normocytic type of anemia may, because of slight technical differences, be considered macrocytic, that is above 94 cubic microns. Study of the mean cell volume alone, without reference to the mean cell diameter, will occasionally lead to error, especially in the hemolytic anemias. Here it is occasionally of some importance to know whether there is a true macrocytic type of anemia or one in which the red-cell diameter is normal but the mean cell volume is greater than normal. A "pseudomacrocytosis" may be associated with a normal red-cell diameter (normocytosis) and an increase in red-cell thickness. This is probably the situation in most of the cases of so-called macrocytic hemolytic anemia.[12]

Kato[13] has created an ingenious triaxial chart which correlates the color index, volume index and saturation index. By use of this chart, Kato states, it is possible to make "an accurate hematologic classification of all types of anemia, so essential a foundation for rational therapy." The chief value of the various indices, aside from the intellectual diversion they might give, rests in the value they may have in the treatment of anemia. For use in infants and young children, Kato[14] has devised a "combination microhemopipette" which is useful in determination of the hemoglobin, hematocrit reading, sedimentation rate, fragility test and prothrombin time.

White Blood Cells

The function of the *lymphocyte* has for many years eluded numerous investigators. By motion-picture studies of supravital preparations of cells which had been grown in tissue cultures, Rich, Lewis and Wintrobe[15] effectively showed that the large cell of acute splenic tumor and of the regional lymphadenopathy of acute infections was an early or large lymphocyte. Enlargement of the spleen or lymph nodes was frequently found to be nonspecific and noninfectious (allergic states, serum sickness). It was suggested that lymphocytes might have something to do with the formation of antibodies to foreign protein. In another study of leukemic blood cells from tissue culture preparations the same workers[16] demonstrated conclusively the very marked physiologic differences between the myeloblast, the lymphoblast and the monocyte-histiocyte. They pointed out the lack of definite information which ordinary supravital preparations may give regarding cellular motility, and the very striking cytologic differences

*With a red-cell count of 1,500,000 and a hematocrit reading of 16, the mean corpuscular volume is 106 cubic microns (macrocytic); another count just as accurate may show a red-cell count of 1,700,000 and a hematocrit reading of 15, the mean corpuscular volume being 90 cubic microns (normocytic).

seen with the combination of the tissue-culture technic and slow-motion cinematography.

The cells of *infectious mononuclears* have been shown by numerous investigations to be abnormal lymphocytes. The word "mononucleosis" is a relic of the days when lymphocytes and monocytes were indiscriminately grouped together as mononuclear cells. The name of the condition might well be changed to infectious lymphocytosis or benign infectious lymphadenosis. Be that as it may, the condition is a very common one and still goes unrecognized in many cases. It is very likely, as stated by Foord and Butt,[17] that only a small proportion of the actual number of cases that occur are properly diagnosed. From the standpoint of differential diagnosis in conditions associated with continued fever, chills and fever, headache with cerebral symptoms, jaundice, abdominal pain (particularly in children), severe sore throat and so forth, the practitioner should be constantly on the alert for the disease. This is particularly true if a college student, a medical student or a nurse contracts some sort of febrile illness. Generalized lymphadenopathy is not always present; in some cases there is only localized adenopathy or splenomegaly. The white-cell count may be low, normal or high. Owing to enlarged mesenteric lymph nodes, abdominal pain may be present; this symptom, associated with a high leukocyte count, may tempt the surgeon to perform an appendectomy. With a low leukocyte count, the possibility of agranulocytosis may be considered. A positive diagnosis can be made in the great majority of cases by careful examination of the stained blood smear, which shows a bizarre type of lymphocytosis with all sorts of queer-staining and unusually shaped lymphocytes. The platelets are abundant, and there is no anemia, both of which are important differential points with respect to leukemia. The serum test (heterophil agglutination test) has proved to be very valuable in confirmation of the diagnosis. Positive tests are usually found as early as the fifth day, although the titer may continue to increase during the first ten or fourteen days. The positivity of the test remains, according to Davidsohn[18] who has done some of the outstanding work with the test, for an average of one hundred and nineteen days. Clinical recovery is rapid — a matter usually of two to four weeks; complete hematological recovery occurs in sixty to ninety days, or even longer in some cases; complete serological recovery is generally slowest. In a certain number of the cases (up to 18 per cent according to A. Bernstein[19]) the serological tests for syphilis may be positive, becoming negative as the condition improves.

Hematologic Reactions to Drugs

The startling therapeutic effects of sulfanilamide and sulfapyridine have at the same time been associated with an increase in the incidence of hematologic reactions. The bone marrow appears to be especially vulnerable to chemicals containing the benzene ring. This vulnerability may manifest itself in the blood as a total effect, with resultant anemia, leukopenia or thrombocytopenia, or in a more selective fashion. Most of the recent investigations have demonstrated that the cyanosis of sulfanilamide administration is due to the development of methemoglobin or sulfhemoglobin. In the work of Harris and Michel,[20] it was found that the degree of methemoglobinemia correlated in general with the blood-sulfanilamide concentration, although other individual factors were undoubtedly important. It was shown by Harris[21] that sulfanilamide in the presence of both hemoglobin and animal tissue resulted in methemoglobin formation in vitro; sulfanilamide incubated with hemoglobin alone failed to cause methemoglobin production. As a rule, one is not concerned with the degree of cyanosis; if this is excessive, however, Campbell and Morgan[22] recommend the administration of methylene blue intramuscularly (400 mg.), intravenously (150 mg.) or by mouth (1 gm.).

Agranulocytosis probably represents, at least in many cases, a sensitization phenomenon on the part of the bone-marrow leukocytes to a chemical which may have become linked to serum protein. Thus far, a test for the susceptibility of a given individual to the sulfanilamide group of drugs has not been developed. The severest reactions probably occur when the drug is given intermittently, although it is possible, as pointed out by Butt, Hoffman and Soll[23] in their animal experiments with amidopyrine, that large doses given over a long period of time may cause toxic hypoplasia of the marrow, with resultant granulocytopenia. Jackson and Tighe[24] analyzed 239 cases of agranulocytosis reported since 1933. In 75 untreated cases the mortality rate was 78 per cent, whereas in 85 cases treated with pentose nucleotides the mortality rate was 35 per cent. The recommendation is made that at least 40 cc. of the latter material be given daily. In the experience of many hematologists scattered throughout the country and personally interviewed, the results with this drug — and with all other measures — in cases of agranulocytosis due to sulfanilamide or one of its derivatives have been disappointing. It would seem that there is no one specific of value in treatment; if the bone-marrow leukocytes

are not irretrievably damaged, the patient will recover; otherwise the effects of therapy in a given case are very dubious.

Leukemoid reactions following sulfanilamide are occasionally seen, and recently an interesting case was observed in which there was first a leukemoid reaction (high white-cell count, myelocytes) followed by a granulocytopenic reaction. At times, one suspects the possibility that acute leukemia itself might have been initiated by the drug. The cases in which acute leukemia follows sulfanilamide administration do not in all probability indicate more than a coincidental relation, although at times a possible causal relation must be suspected. Thrombocytopenic purpura and complete aplastic anemia are rare with sulfanilamide. About fifty cases of the former condition have, however, been reported following the use of the sedative Sedormid.

Pernicious Anemia

Wintrobe, Samter and Lisco[25] have produced a close analogue of pernicious anemia in young suckling pigs by the use of a diet deficient in the various factors of the B_2 complex. The feeding of yeast was sufficient to prevent the anemia, but in the absence of this substance a macrocytic anemia hematologically comparable to that seen in pernicious anemia was observed, together with neurologic lesions and a hyperplastic bone marrow. No response occurred when nicotinic acid, riboflavin or vitamin B_1 was administered, but reticulocytosis and marked improvement in the anemia occurred when yeast was given. These experiments are confirmatory of the well-known theory that pernicious anemia is a deficiency disease, perhaps concerned with a long-standing dietary deficiency, either as such or conditioned by an abnormality of the gastrointestinal tract. Alsted[26] reports a clinical case of "exogenous pernicious anemia" which developed as the result of a totally inadequate diet, although the gastric juice contained free hydrochloric acid; an excellent therapeutic result was obtained without the use of liver extract. Whatever the cause, deficiency in the liver-extract principle results in a peculiar hyperplastic state in the bone marrow. This is characterized by an increase in primitive erythroblasts (erythrogones) and the presence of characteristic megaloblasts and of abnormally shaped metamyelocytes. Israels[27] confirms the work of Dameshek and Valentine[28] on these points.

The appearance of the gastric mucosa in life was studied by Schindler and Serby[29] in 23 patients. All the untreated cases presented superficial gastritis, atrophic gastritis or patchy atrophy. In 12 cases the condition of the gastric mucosa after treatment was greatly improved. From these observations, it was postulated that two separate disorders might be present in pernicious anemia: a primary disorder of the cells producing the antianemic factor, and a gastritis which might or might not heal when the deficiency state is eliminated. The condition of the tongue and that of the gastric mucosa are frequently related. That pernicious anemia is also a hemolytic anemia has recently been stressed by Rhoads and Miller.[30] To explain this on a deficiency basis is difficult, unless one postulates, as Rhoads has done, that in the presence of a deficiency state certain toxic processes might become unusually active in hemolysis. In the therapy of the disease, Meulengracht[31] found that parenteral therapy was too expensive for most Scandinavians and of no greater potency than Pylorin, which is derived from the mucosa in the region of the pylorus. This material, apparently twice as potent, gram for gram, as Ventriculin, was effective in maintaining a normal blood picture and in preventing neurologic involvement. In this country it is possible that we are too free in the use of parenteral therapy and that a certain number of patients would probably do very well on oral therapy alone. At times, this method of administration becomes necessary when the patient develops severe reactions to injected liver extract. If this should eventuate, three courses are open: to change from the ordinary swine-liver extract to beef-liver extract*; to desensitize the patient by giving gradually increasing doses; and to give liver, liver extract or gastric extract by mouth. In the presence of neurologic lesions, parenteral therapy must of necessity be continued. It should be noted that even at a normal red-cell level, neurologic lesions may still be present. These may well respond to intensive parenteral therapy. This is particularly true of lesions in the posterior columns. In my hands, highly concentrated and refined liver extracts, which the patients like because of their small bulk, are highly effective, perhaps even more so than are the more dilute, cruder types. This indicates that what the patient with neurologic involvement needs is plenty of liver-extract principle and that other factors, including the vitamin B complex present in the dilute liver extracts, are not ordinarily essential.

Iron Deficiency Anemia

A number of investigators have recently pursued various aspects of the problem of iron metab-

*Campolon Liver Extract (Winthrop) or Lederle Beef-Liver Extract (obtainable on request) may be used.

olism. Josephs[32] found that during the first months of life there was a tendency to a negative iron balance (loss of iron from the body); a positive iron balance was later established. Whereas normally about 60 per cent of the ingested iron was absorbed, a slightly diminished retention of iron was present during infections and in vitamin D deficiency. In anemia, the organic iron of the tissues appeared to be retained; at times it became unavailable for use by the marrow. Inorganic medicinal iron was, however, readily available. An interesting study with "marked" or radioactive iron was made by Hahn, Bale, Lawrence and Whipple[33] in anemic dogs. In the normal dog, iron was absorbed in only negligible amounts, but in the anemic animal it was promptly assimilated, absorption taking place through the mucosa of the small intestine, whence the iron is transported in the plasma. Within a few hours, in the anemic dog, some of the absorbed iron was found in the red cells of the blood. The reticuloendothelial cells of the spleen and marrow took up large quantities of iron, in this manner acting as a reserve store of readily available and utilizable iron. Moore, Minnich and Welch[34] present a very interesting group of observations dealing with changes in the serum iron and in the "easily split-off" blood iron. Serial observations during iron therapy gave a dynamic picture of the rapidity of transportation and absorption of ingested iron. The serum-iron absorption curves were higher following ingestion of ferrous than of ferric salts; this was particularly true of the water-soluble, highly ionized ferrous salts. Differences in gastric acidity exerted no measurable effect on serum-iron absorption curves when inorganic iron was given. Ingested iron is probably acted on by the free hydrochloric acid of the gastric juice, which may dissolve and ionize it. In the duodenum, the ionized iron is probably reduced from the ferric to the ferrous form. Absorption then takes place as ferrous iron, largely in the upper part of the small intestine.

Kennedy[35] conducted a study on the incidence of anemia in women of the low-income class in Montreal. He found that menstrual loss was of definite importance in the development of anemia, and that the low iron content of the diet necessitated by poverty was often insufficient to keep pace with the demands of menstruation and repeated pregnancies. Bethell, Gardiner and MacKinnon[36] studied the influence of iron and the diet on the blood in pregnancy. The basic diet recommended for pregnancy, as formulated by the League of Nations Technical Commission, provides a daily protein intake of approximately 80 gm., including meat, eggs and adequate quantities of vitamins A, B (complex), C and D. Anemic women receiving iron (ferrous sulfate, 15 gr. daily) showed much higher hemoglobin and red-cell values than did those not receiving this medication. Patients without anemia did about the same whether or not iron was given.

The chronic primary or idiopathic hypochromic anemia, which is an iron-deficiency state occurring usually in adult women, is for the most part associated with menorrhagia, multiple pregnancies and inadequate iron intake, plus the added and very important factor of an impaired gastric mucosa, as shown by achlorhydria and directly by visual inspection with the gastroscope. Occasional cases of this sort are seen in men, but they are extremely rare, and the question of past or occult bleeding from the gastrointestinal tract should be thoroughly investigated. The response to inorganic ferrous iron (ferrous sulfate, 15 gr. daily) in these cases is dramatic.

Hemolytic Anemias

Although the diagnosis of acquired hemolytic jaundice or anemia has for some reason gone out of fashion in recent years, there are indications that it might well be revived. A tentative classification of the hemolytic anemias is as follows:

- Congenital
  - Acute ("hemolytic crisis")
  - Chronic
- Acquired
  - Known cause
    - Infections (Welch bacillus, malaria and so forth)
    - chemicals (sulfanilamide and so forth)
  - Symptomatic (carcinomatosis, Hodgkin's disease, lymphosarcoma, leukemia and so forth)
  - Idiopathic (with or without hemolysins or autoagglutinins in the blood serum)
    - Acute
    - Subacute
    - Chronic

Barker[37] and Vaughan and Saifi[38] emphasize the importance of determinations of the daily fecal urobilinogen output as a measure of the degree of hemoglobin destruction. In hemolytic anemias, including pernicious anemia, the urobilinogen output is greatly increased. The latter is a far more sensitive test than the urinary urobilinogen output, at least as measured by the ordinarily used Wallace-Diamond technic.

An excellent discussion of the spherocyte and its relation to hemolytic anemia is presented by Haden[39]; the relatively thick spherocyte which is seen in various hemolytic syndromes cannot take

up very much water when placed in hypotonic solutions of sodium chloride, and therefore bursts (complete hemolysis) long before the more normal biconcave disk. Conversely, a very flat cell is more resistant because it can imbibe a large quantity of water before bursting. Heilmeyer[40] and Schwartz and I[12] disagree with the current conception that the bone marrow is at fault in congenital hemolytic jaundice and produces thick cells or spherocytes. Heilmeyer believes that the spleen is responsible for the spherocytosis. Dameshek and Schwartz have demonstrated that anemia with spherocytosis may be experimentally produced by hemolysins; on this and other grounds, they have evolved the conception that hemolytic anemia of various types may be due to hemolysins of different types acting in various "dosages." Spherocytosis and increased saline fragility may thus be taken simply as indicative of the presence of a hemolytic process. The spherocyte is the forerunner of hemolysis. Because spherocytes are rounder than normal, they have difficulty in piling up in rouleaux in fresh preparations. Examination of fresh preparations of blood may thus be diagnostic of hemolytic anemia, as pointed out by Dameshek.[41] The abnormal rouleaux are short and form very poor aggregates; thus in hemolytic anemias the sedimentation rate is apt to be slow. Vaughan[42] noted that following splenectomy in congenital hemolytic jaundice the red cells often became normal in size, although they still retained an abnormal fragility. The loss in spherocytosis indicated to Vaughan that the spleen has some effect in altering the shape of the red cell; the persistence of increased fragility might indicate, however, a fault in red-cell formation. She suggests, therefore, that in congenital hemolytic jaundice there may be disturbances in both splenic and bone-marrow function. According to Bergenhem and Fahraeus,[43] the spleen is the "incubator of the body," and within its relatively static confines, the blood cells are acted on by a substance normally present in plasma, namely "lysolecithin." This substance, which may be responsible for normal red-cell destruction, is said to have the capacity to change biconcave red cells to spherocytes and thus to inhibit the sedimentation rate. Singer[44] has developed a micromethod for testing this normal lysin in the blood; he found no increase in lysolecithin in the blood of cases of hemolytic anemia. Because the spherocytes of congenital hemolytic jaundice can be hemolyzed by lysolecithin in high dilution, whereas spherocytes from other conditions behave like normal erythrocytes, Singer postulates that spherocytes, although morphologically identical, may be physiologically different. This has been the point of departure for the concept of differential fragility, as proposed by Dameshek, Schwartz and Singer.[45] By testing the same red cell against different types of lysins, it is possible that different types of spherocytes may be discriminated and that, in this way, clues may be obtained as to the cause of the spherocytosis.

For some reason the diagnosis of acquired hemolytic icterus or anemia has been avoided in recent literature, and has been to a great extent superseded by such terms as Lederer's anemia and macrocytic hemolytic anemia. The eponymic term Lederer's anemia is probably not justified, because the condition was described in case reports by various European writers for many years before Lederer's descriptions in 1925 and 1930. The term macrocytic as applied to these cases is also probably not entirely justified, because the mature red cells in this condition are not macrocytic but either normal in size or microcytic. The macrocytosis is usually more apparent than real, being due to the large number of immature polychromatophilic reticulocytes, which are larger than the normal mature red cells, as well as to increased thickness of the erythrocytes. Watson[46] uses the term macrocytic hemolytic anemia as synonymous with acquired hemolytic jaundice. In most of his cases there was true macrocytosis, but this was probably due to the fact that cirrhosis of the liver, Hodgkin's disease or leukemia was present. Autoagglutination of the red cells, as occurring in acquired hemolytic jaundice, was stressed by Widal and his collaborators between 1907 and 1914. It has recently been rediscovered and has been reported in a number of cases of acute and macrocytic hemolytic anemia. Antopol, Applebaum and Goldman[47] report this phenomenon, which may make blood-grouping tests difficult, in 2 cases of acute hemolytic anemia following the administration of sulfanilamide.

One of the most dramatic events in medical practice is the effect of splenectomy in a patient seriously ill with the hemolytic crisis of congenital hemolytic icterus or with acute (acquired) hemolytic anemia. Within a few hours after operation, there is usually a remarkable improvement both in the appearance of the patient and in his sense of well-being. Before the operation of splenectomy is decided on, the effect of one to three transfusions of carefully matched citrated blood of the same blood group given slowly may be tried—"bank" blood should not be used. If evidence of hemolysis continues, splenectomy should be performed without further delay. The giving of too

many transfusions may result not only in severe reactions but in overburdening the circulation; too much delay may result in a fatal outcome. The acute hemolytic crisis, whether congenital or acquired, requires careful and intelligent handling, and represents as much of a emergency as a case of diabetic coma.

Of 15 cases recently observed by me, 8 patients made dramatic and sustained recoveries, 5 died shortly after operation, and 2 relapsed. Of the latter, one has died and the other has improved after a second operation in which a dermoid cyst was removed. Andrus and Holman[48] recommend the injection of 1 cc. of adrenalin just before delivering the spleen. The resultant splenic contraction is said to facilitate the delivery of the organ into the wound, and also expresses some of the excess splenic blood into the general circulation. They report seventeen splenectomies in hemolytic jaundice without an operative death. Thompson[49] discusses typical and atypical hemolytic anemias and the end results of splenectomy. The results were uniformly good (except in 1 case) in the typical group, but were poor in the atypical group, including cases of acquired hemolytic jaundice.

Atypical Hemolytic Anemias

Sickle-Cell Anemia

Diggs and Bibb[50] describe the red-cell characteristics in sickle-cell anemia. The percentage of typically sickled cells is not related to the severity of the anemia. "Mexican-hat cells" (Haden and Evans[51]) or "target cells" (Barrett[52]) are common; these cells are shaped like a bull's-eye or target in stained preparations, and are more resistant to hypotonic solutions of salt than are the normal erythrocytes. Arena[53] reports 5 cases in children, notable because of the appearance of serious cerebral vascular disturbances. Capillary stasis due to distortion and agglutination of red cells, together with other factors such as fever and infections, probably contribute to the development of arterial thromboses.

Erythroblastic Anemia

Atkinson[54] points out the various clinical features of Cooley's anemia, usually a disease of young children and ordinarily fatal before puberty. The 2 cases described have been followed for thirteen years. The girl, aged twenty, began to menstruate at sixteen and is asymptomatic; no nucleated red cells have recently been seen. This is apparently a very mild case, which may be more or less "burnt out." The patient's brother, aged seventeen, has had a much more stormy course, perhaps because splenectomy was done at the age of six. Showers of nucleated red cells have persisted without much change over the years. The treatment has consisted of iron in large doses. The author quotes Caminopetros,[55] who found that certain relatives of individuals with the disease showed an increased resistance of the red cells to hypotonic solutions of salt; these individuals, Atkinson believed, might be the carriers of the disease. The red cells of Cooley's anemia, unlike those of congenital hemolytic jaundice and like those of sickle-cell anemia, show a decreased fragility.

Polycythemia

Rosenthal and Bassen[56] present an interesting study on the course of polycythemia based on an analysis of 13 cases. The disease may be asymptomatic and discovered accidentally. It may be of many years' duration. Extremely high platelet counts were present in about 30 per cent of 75 cases; in these thromboses were common. These authors lay much stress on the evidences of leukoblastic activity and on the possibility that leukemia will eventually develop in many cases. "Spent" polycythemia may be associated with a chlorotic (low-hemoglobin) tendency, high platelet or leukocyte counts, or osteosclerosis. Possibly belonging to the latter group of cases are the 2 cases of "leukoerythroblastic anemia" and myelosclerosis reported by Vaughan and Harrison.[57] Both their patients had initial polycythemia, but when studied several years later they showed marked splenomegaly, irregular density of the spongiosa of the bones, anemia with leukocytosis, thrombocytosis and nucleated red blood cells, increased saline fragility and fibrosis of the marrow. Miller[58] reports on the high incidence of coronary-artery thrombosis in polycythemia vera as based on 7 cases which came to postmortem examination; of these 3 showed the evidences of coronary-artery occlusion.

Haden[59] discusses the red-cell mass in polycythemia with relation to diagnosis and treatment. The red-cell mass is determined from knowledge of the volume per cent of packed red cells (hematocrit reading) and the total blood volume. The red-cell count does not accurately measure the total increase in the mass of red cells within the body since the red cells are apt to be small and hypochromic, whereas the red-cell mass per kilogram is the most sensitive indicator. Haden believes that the treatment of polycythemia should be based on the total red-cell mass. Dameshek, Henstell and Schwartz[60] have come to similar conclusions, except that they believe that in practice the use of the hematocrit reading for an indication of the total red-cell mass is justifiable. Therapy should be directed to lowering the hematocrit

reading and maintaining it at a normal level (approximately 46 per cent). After the establishment of an iron-deficiency state by repeated venesections (usually two per week for three or four weeks) of 500 cc., continuation of the iron-deficiency state may be maintained by a diet low in iron. The red-cell count may rise in three or four months, but so long as the hematocrit reading remains at an essentially normal value, no further treatment is necessary. Ordinarily, cases will go along for eight to fifteen months between series of venesections.

The use of a low-iron or low-protein diet alone has not been found effective in our cases, but Herzog and Kleiner[61] report striking results in 19 cases with a diet extremely low in animal protein. Andersen, Geill and Samuelsen[62] treated a case of polycythemia with x-rays over the Brunner-gland region of the stomach and duodenum, with an excellent result. Their purpose was to diminish secretion in the area in which the intrinsic factor is formed. The authors believe that this method is more rational than that of treating the bone marrow with x-rays. My experience with x-ray therapy in this disease has been disappointing; furthermore, it seems unwise to expose an individual with essentially normal tissues to x-ray therapy, which might at some future time result in neoplastic proliferation.

Hemorrhagic States

Blood Clotting

Seegers and his co-workers[63] at the University of Iowa describe further work in the purification of thrombin. The addition of calcium and thromboplastin to a prothrombin solution resulted in a crude thrombin which could be further purified. One cubic centimeter of a 1 per cent solution of this purified thrombin was effective in clotting 1 cc. of blood in two seconds. By the use of a thrombin solution spray, these workers were able to stop the oozing from incised liver, bone and brain tissue. Its application to clinical hemorrhagic conditions has thus far been slight, but the further results of these investigators will be well worth watching.

The clotting of blood is taken up from another direction by Ferguson and Erickson,[64] who have studied the action of trypsin. This enzyme can clot citrated plasma without added calcium or cephalin. Trypsin may be one of a series of thromboplastic enzymes which cause the mobilization of calcium and thromboplastin about prothrombin, with resultant formation of thrombin. Ferguson and Erickson have also been able to activate the prothrombin of hemophilic "globulin substance" to normal thrombin, with resultant clotting, by the addition of pure crystalline thrombin. The plasma of individuals with hemophilia may be deficient in thromboplastic enzyme.

Hemophilia

In last year's review the studies by Lozner and Taylor[65] on the coagulation defect in hemophilia were presented. At that time their experiments revealed a deficiency in the globulin fraction of the plasma. "Globulin substance" prepared from normal human plasma was found to hasten the clotting time for hemophilic blood, both in vitro and in vivo. After several injections of this substance, however, a refractory phase occurred so that the clotting time rose to its original level despite continued injections. When normal or lyophilized plasma was injected the refractory period was ended, indicating that whole plasma contained a substance that was effective.

In a more recent publication, Lozner, Kark and Taylor[66] state that normal serum from which prothrombin and fibrinogen had been removed was still capable, when injected, of causing a prompt fall in the coagulation time of hemophilic blood, both in vitro and in vivo. It was suggested that the loss of effectiveness of the globulin substance might be the presence of a factor in normal plasma which was lost in the acid precipitation of the globulin substance. Therefore, globulin was prepared by dialysis by Lozner and Taylor,[67] and such a preparation of euglobulin was found to resemble normal human plasma in its ability to maintain in hemophilia a reduced level of the blood-coagulation time when injected intravenously every six hours. One hopes that in time the results of these investigations will be to produce a substance which when injected periodically into a patient with hemophilia will mantain his blood at a normal coagulation level.

Vitamin K

During the last few years, outstanding advances have been made in the troublesome and dangerous hemorrhage of jaundice. Quick[68] deserves great credit for the initiation and development of these studies. In obstructive jaundice or biliary fistula, where bile salts do not reach the intestinal tract, poor absorption of fat-soluble vitamins results. Rarely, a severe dietary deficiency may lead[69] to a lowering of the vitamin K content of the body (Kark and Lozner). In the absence of fat-soluble vitamin K there is lowering of the plasma prothrombin, with a resultant hemorrhagic tendency. The plasma prothrombin level can be sustained by giving vitamin K concentrates and bile salts

by mouth. Blood transfusion is a rather inefficient method of combating the bleeding tendency due to hypoprothrombinemia, as its effect is slight and transient. After a 600-cc. transfusion in one patient, Stewart[70] found an increase of only 6 per cent of plasma prothrombin.

Rapid progress has been made in the chemistry of vitamin K. A rather large number of compounds with vitamin K activity have been found, and several of these have been identified and synthesized. When oral administration is uncertain because of vomiting or severe diarrhea, a highly purified preparation or one of the recently developed synthetic products may be used. In the synthesis of such preparations, Doisy and his collaborators[71] at St. Louis and Fieser and his co-workers[72] at Harvard have done outstanding work. Frank, Hurwitz and Seligman[73] report 2 cases treated with Fieser's synthetic vitamin K. In both cases, a single intravenous injection of the substance resulted in a fall of the prothrombin clotting time to normal within a few hours.

The mechanism by which prothrombin is formed and its dependence on vitamin K are not understood. The liver has been regarded as the site of prothrombin formation because hepatoxins, such as chloroform, cause a plasma-prothrombin deficiency, and because some patients believed to have severe liver damage have failed to respond to large amounts of vitamin K and bile salts. In the dog, total hepatectomy causes a rapid fall in plasma prothrombin.

Until recently, the mechanism in the condition known as hemorrhagic disease of the new born has not been understood. Quick[74] suggested a prothrombin deficiency. In a study of 20 newborn infants, Waddell and Guerry[75] showed that the prothrombin clotting times were unusually high between the second and sixth days of life, corresponding to the time at which hemorrhagic disease almost always manifests itself. Administration of vitamin K concentrates orally kept the prothrombin and blood-clotting times normal. Routine use of such therapy in the infant or possibly in the mother late in pregnancy may be the answer to the prophylaxis of many cases of intracranial hemorrhage during birth and of the occasional fatal bleeding following surgical procedures, such as circumcision, early in life.

Owen, Hoffman, Ziffren and Smith,[76] who with Quick have contributed so much to our knowledge of vitamin K, have also simplified the prothrombin clotting test so that an easy bedside method is now available which correlates well with the more complicated procedures. It should be emphasized that vitamin K is of no value in the therapy of any hemorrhagic condition except that of prothrombin deficiency. Thus it has no effect whatever in hemophilia, in thrombocytopenic purpura or in any other type of purpura.

Thrombocytopenic Purpura

Very little that is new has been written of thrombocytopenic purpura in the past year. Some new cases of purpura caused by the taking of Sedormid are reported. McGovern and Wright[77] point out that Sedormid may cause a serious hemorrhagic syndrome. They advise restriction of its sale except on a physician's prescription and caution on the part of the physician in recommending its use. In 1938, a slight sensation was occasioned by the appearance of data purporting to show that splenic extracts from cases of thrombocytopenic purpura resulted in marked reduction in platelets in rabbits. The substance causing this reduction was named "thrombocytopen."[78] Numerous investigations undertaken in an attempt to confirm this phenomenon have, however, proved uniformly unsuccessful.[79]

113 Bay State Road

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTEMORTEM AND POSTMORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 26241

PRESENTATION OF CASE

First Admission (July 30 to August 21, 1935). A twenty-three-year-old housewife was admitted to the hospital, complaining of painless swelling of the right neck.

Approximately sixteen months before admission, in March, 1934, the patient first noted a constant, non-radiating, dull pain, located in the right side of the neck, below the angle of the jaw, and over an area where there was a palpable, marble-sized mass. Within a few weeks the soreness passed away, but the mass persisted, gradually increasing in size. She continued her work and detected little change in her general condition until about nine months before admission, when she developed a chronic cough, productive of small amounts of mucoid sputum; at the same time she began to tire easily and lose weight. Seven months before entry pain in the region of the right neck returned but again passed away within two weeks' time. A similar discomfort then appeared in the region of the right axilla, over a palpable, firm, pecan-sized mass. This discomfort continued, and the mass gradually enlarged. Two weeks before admission a dull pain (without palpable mass) appeared below the angle of the left jaw. Because of general malaise, weakness, easy fatigability and the gradually enlarging axillary and neck masses, the patient entered the hospital. It was stated that all the masses mentioned had grown slowly and had become firmer, but had remained non-tender and non-inflamed. The overlying skin had remained freely movable, as did the masses beneath it. She denied ever having had tuberculosis, periods of fever, chills, night sweats or hemoptyses.

The physical examination revealed a well-developed and well-nourished woman in no apparent discomfort. The skin showed a chronic generalized eczema, with lichenification in the antecubital spaces, with residual dirty-brown pigmentations over the trunk and limbs, and with patches of depigmentation over the outer aspect of the left thigh, left popliteal space, and the left knee. The right neck bulged, and there was fullness over the right shoulder and right anterior upper chest. This was the result of the presence of various-sized ("olive to egg"), hard, discrete, non-tender masses in the region. They were relatively fixed in the neck but movable elsewhere. There were several olive-sized, hard, discrete, movable nodes in the right axilla. The right pectoral and trapezius muscles also contained several more. The trachea was pushed to the left by a mass which filled the suprasternal notch. The inguinal regions were negative. Examination of the heart was negative, except for the presence of a soft blowing systolic murmur at the apex. The blood pressure was 120 systolic, 64 diastolic. The lungs showed increased tactile fremitus, vocal fremitus and breath sounds in the entire upper half of the right lung anteriorly and posteriorly. The abdomen was negative. The liver and spleen were not palpated. The pelvic examination was negative.

The temperature was 99.2°F., the pulse 90, and the respirations 22.

Examination of the blood showed a red-cell count of 4,900,000 with 70 per cent hemoglobin (Tallqvist), and a white-cell count of 20,000 with 80 per cent polymorphonuclears, 8 lymphocytes, 9 monocytes, and 3 eosinophils; the smear was normal. The stools were negative. A blood Hinton test was negative. A basal metabolic rate was +17 per cent.

Roentgenograms of the chest showed an ill-defined area of consolidation close to the right hilus, and a fusiform area of increased density in the anterior part of the right middle lung field corresponding to the septum between the upper and middle lobes. There was marked soft-tissue swelling of the right supraclavicular area, and some swelling of the right axilla.

The patient remained in the hospital for twenty-three days during which time she ran a Pel-Ebstein type of fever, ranging from 99 to 101°F. each day. On the fifth hospital day a biopsy of a cervical node was done. The pathological report was lymphoblastoma, Hodgkin's type. X-ray treatment was begun before her discharge, August 21, 1935 (Table 1).

Second Admission (June 9 to 23, 1936). The patient had received three courses of x-ray treatment since her discharge from the hospital.

A film taken May 2, 1936, showed appreciable diminution in the area of dullness at the right lung root. She entered for the termination of a pregnancy of about two months' duration. Hysterotomy and sterilization were performed four days after entry. All the laboratory findings at this time were negative.

Between the second and final admissions many x-ray films were taken and reported as follows. June 29, 1936: the indefinite rounded area of diminished density within the chest was still present and appeared smaller. December 10, 1936: the process was slightly less extensive, and the left lung remained clear. January 30, 1937: the appearance of the right lung field remained unchanged; on the left side, however, there were two irregular areas of density in the lower lung field, one extending from the level of the fourth rib to the fifth interspace anteriorly, the other lying just above the costophrenic angle. February 13, 1937: the area of consolidation on the left had markedly cleared. June 19, 1937: there was some increase in dullness laterally from the right hilus shadow. October 23, 1937: the process on the right side had not appreciably changed; there was a new ovoid lesion, measuring about 2 by 1.5 cm., close to the left border of the heart. September 18, 1937: extensive density still extended out from the right hilar region; the right diaphragm was markedly elevated in its medial portion; the left lung remained clear; there was considerable dorsal scoliosis. February 19, 1938: considerable dense, irregularly mottled infiltration was noted radiating from the right hilus involving the medial portions of the right upper and middle lobes; also, what appeared to be a round cavity which measured approximately 1 cm. in diameter was made out at the level of the sixth interspace posteriorly; a large triangular dense shadow filled the right lower medial chest anteriorly. June 19, 1938: there was extensive consolidation with fibrosis along the medial aspects of the right lung with displacement of the lung to the right and compensatory emphysema of the remaining lung field on the right; a small focus of consolidation was noted at the fifth interspace on the left side laterally. August 27, 1938: slight improvement in the appearance of the chest was observed, but the cavities were still present. October 29, 1938: there was a destructive process in the right upper lobe with collapse of the right lower lobe, and a localized area of consolidation at the left lower lung field laterally, probably corresponding to the anterior portion of the lower lobe.

TABLE 1. *X-Ray Treatment, August, 1935, to April, 1939, Inclusive.*

DATE	ANTERIOR MEDIASTINUM	POSTERIOR MEDIASTINUM	RIGHT NECK	RIGHT AXILLA	RIGHT ANTERIOR CHEST	RIGHT POSTERIOR CHEST	LEFT NECK	ABDOMEN	ANTERIOR NECK	POSTERIOR NECK	RIGHT LATERAL CHEST
	r	r	r	r	r	r	r	r	r	r	r
1935:											
August	600	600	600	600							
September			600								
December			600	600							
1936:											
March	900	900									
June to July			600		600	600					
September				500							
December	1200	1200	600				600				
1937:											
April				600							
June			600	600	600	600					
August								900			
September					900						
October				600							
1938:											
January	900	900									
February			900								
April									600	600	
June									900	900	
September to October				600							
October	1500	1500									
1939:											
April											300
Totals	5100	5100	4500	4100	2100	1200	600	900	1500	1500	300

Final Admission (April 7 to 11, 1939). Since her discharge in June, 1936, the patient had received frequent x-ray treatments which had apparently produced regression in many of the diseased areas previously noted. In June, 1937, the patient began to complain of increasing weight loss and hemoptysis. There developed a reappearance of matted nodes in the right neck region. In August, 1937, or about one and a half years before the final admission, the patient developed discomfort and pain in the right shoulder, with weakness of the right arm, and a classical Horner's syndrome on the right. The arm gradually became worse, and

the patient showed much emaciation. After three months of progressively increasing discomfort and pain in the arm, it became completely paralyzed, and a wrist drop developed. The cough became more severe and was productive of considerable amounts of sputum. In spite of continuing weakness, weight loss and easy fatigability, she was still able to attend to her housework. Under x-ray therapy the use of the right arm began to return. In December, 1938, the paralysis had markedly subsided, the weight had increased slightly, and the general condition improved. However, one month later, in January, 1939, her activities became definitely limited because of shortness of breath, progressively increasing weakness and the appearance of chills, fever, night sweats and upper-respiratory infections. The dyspnea became so severe that she noted it on coughing or talking, but there was no chest pain. She was given x-ray therapy to the right chest region, as had been done for a number of months previously, but in spite of all efforts, she went progressively downhill and was admitted to the hospital for terminal care.

Physical examination revealed a thin, emaciated, cachectic young woman in moderate respiratory distress. There was dullness to flatness, with diminished fremitus and absent breath sounds over the right anterior chest, and coarse, moist inspiratory and expiratory rales with increased breath sounds were heard over the anterior and posterior left chest. Resonance, with bronchial breathing, was heard in an elliptical area overlying the medial border of the right scapula, just inferior to its spine and extending to the eighth rib below. Surrounding this area posteriorly the chest was dull to flat to percussion and the breath sounds were diminished to absent. The heart sounds were almost inaudible due to rales which masked them. The blood pressure was 98 systolic, 68 diastolic. There was a slightly tender, stony-hard, nodular, laterally movable mass in the abdomen in the region about the umbilicus. There were many hard, non-tender, bilateral cervical and supraclavicular, pea-sized to marble-sized masses. Neurological examination revealed that the right pupil (2 mm.) was smaller than the left (5 mm.). Both pupils reacted to light and accommodation. The external ocular movements were normal and full. The fundi were negative. The right arm was found to lack sensation. Motions of the right shoulder were limited. The right elbow could be flexed only to a right angle. The muscles of the arms were atrophic.

The temperature was 101°F., the pulse 142, and the respirations 25.

Examination of the blood showed a red-cell count of 5,400,000 with 82 per cent hemoglobin, and a white-cell count of 17,300 with 93 per cent polymorphonuclears, 6 per cent lymphocytes and 1 per cent eosinophils. Stools were guaiac negative. The blood protein was 6.6 gm. per 100 cc. Roentgenograms of the chest showed that there was an increase in the destructive process in each side of the lung. The right upper lobe was completely involved, as were the greater portions of the lower and middle lobes. The heart was markedly displaced to the right, due to partial atelectasis. There were several small areas of cavitation visible in the region of the upper and middle lobes. There was an increase in the parenchymatous process of the lung on the left side.

The patient rapidly went downhill and died four days after admission.

Differential Diagnosis

Dr. Frederick W. O'Brien:* I think it is Boyd who quotes Goethe to the effect that what one knows, one sees. Since there was a positive biopsy in this case, I am prejudiced from the start. If you recall, the first film gives the impression of a right upper-respiratory infection with some interlobar fluid. The blood picture was as characteristic as is any blood picture of Hodgkin's disease in the early stage. Sometimes you see more of an eosinophilia than is indicated here. We read in the history, "The liver and spleen were not palpated." I do not know precisely what that means.

Dr. Tracy B. Mallory: They were looked for and not found.

Dr. O'Brien: It is not too unusual for the spleen and liver to appear normal to palpation in Hodgkin's disease. The fever curve referred to on the patient's first admission might make one think of the Pel-Ebstein form of Hodgkin's disease but could go equally well with tuberculosis. Tuberculosis and Hodgkin's disease in the same patient occur in young persons but are rather rare in adults. There is nothing said here about the character of the nodes. I presume because they were non-tender and non-inflammatory that they were not tuberculous nodes. Were any sputum examinations done in this case, and, if so, were bacilli found?

Dr. Mallory: They were never demonstrated, I can assure you. I think we can be sure they were looked for.

Dr. O'Brien: Following x-ray treatment there was an apparent change in the size of the area of infiltration seen close to the right hilus in succeeding films, however, I think it is more apparent

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than real as one compares the series. If we look closely the suspicion of abscess formation arises. Following x-ray therapy one might expect some clearing of such a lesion. I am inclined to rule out tuberculosis because the lesions in the films which show a definite contralateral spread cleared up almost overnight after x-ray treatment. Furthermore, there was a Horner's syndrome in this case. I am not familiar with its occurrence in pulmonary tuberculosis. Brucellosis comes to mind in the differential diagnosis. Parsons and Poston* at Duke University recently reported 4 cases of brucellosis where the histopathology of the nodes was believed identical with that of Hodgkin's disease. Brucellosis, however, does not show the progressive lung changes seen here and I believe only affects the lungs terminally. Among the unusual things one must consider actinomycosis. It too may be a long-standing process but, as I understand it, does not involve the nodes, may involve the chest wall and is always accompanied by a sinus. In the presence of supraclavicular nodes, Horner's syndrome and the roentgen picture, carcinoma is a possibility. There is no evidence of rib destruction, which is seen in primary-sulcus tumor. Oat-cell cancer of the lung may improve under irradiation, but in any type of lung cancer I should not expect a generalized adenopathy of axillas, groins and mediastinum such as we have in this case, so that I am forced back to a diagnosis of Hodgkin's disease with infection. I say with infection because in the later films you see what appears to be cavity formation in an otherwise dense right upper lobe, and so far as I can learn, cavity formation does not occur in Hodgkin's disease except in the presence of superimposed infection. Interstitial involvement of the lungs occurs in about 30 per cent of the cases of Hodgkin's disease. One thing I should like to ask — I see no mention of it — is whether or not the nodes regressed under x-ray treatment.

Dr. Edward A. Gall: They did originally. Later on the mass in the neck subsided only slightly.

Dr. O'Brien: One might well wonder whether the changes seen on the film in the right upper-lung field were brought about by overenthusiastic radiation. When you have a patient as ill as this one was and as badly in need of attention, it is difficult to treat the patient otherwise, but I think sometimes that we overirradiate. The question arises here whether irradiation produced the changes we see. They are not characteristic of any pulmonary fibrosis that I have recognized as such following radiation. So I am forced again to conclude that we are dealing with Hodgkin's disease with superimposed infection.

Dr. Mallory: Some of the audience may be interested in hearing more about this last question that Dr. O'Brien has raised. What dosage of x-rays is necessary to produce x-ray pneumonitis?

Dr. O'Brien: I do not believe anyone knows. The individual case differs. We have had patients who received more irradiation than this woman with only a resultant fine pulmonary fibrosis, certainly nothing similar to what we see here. I do not believe this was all due to radiation.

Dr. John H. Talbott: I should like to raise the question of whether or not this may be acanthosis nigricans with peripheral manifestations. The skin pigmentation suggests that diagnosis so far as the first physical examination was concerned.

Dr. Gall: She had had that all her life.

Dr. Lingley: I should like to ask Dr. O'Brien if he thinks it is necessary to postulate infection because of the presence of cavities in the lungs.

Dr. O'Brien: I have no authority for it, outside of talking to Dr. Frederic Parker, Jr. His belief is that you do not see cavitation in Hodgkin's disease without superimposed infection.

Dr. Donald S. King: We have seen cavities disappear under x-ray treatment.

Dr. Lingley: Yes. I remember 2 cases of Hodgkin's disease which were treated by x-ray with disappearance of the cavities, but we were never able to find infection. One of these cases came to postmortem and was still straight Hodgkin's disease.

Dr. King: Of course you did not prove that it was not infected at the time.

Dr. Lingley: There is no characteristic fluid level which we should expect, and no pus or temperature or anything else to go with it.

Clinical Diagnosis

Lymphoblastoma, Hodgkin's type, generalized.

Dr. O'Brien's Diagnosis

Hodgkin's lymphoma with pulmonary invasion and superimposed infection.

Anatomical Diagnoses

Lymphoblastoma, Hodgkin's type, involving lymph nodes and lungs.
Fibrosis of lungs: probably radiation pneumonitis.
Ichthyosis.
Hydropericardium.
Hydrothorax.

*Parsons, P. B., and Poston, M. A.: The pathology of human brucellosis: report of four cases with one autopsy. *South. M. J.* 32:7-13, 1939.

Pathological Discussion

Dr. Mallory: This is a case where the pathologist, too, does not escape without a good many perplexities and troubles. When this patient came to autopsy the lungs presented a very extraordinary picture, unlike anything we had ever seen before. All five lobes showed lesions of one sort or another, and they differed in all five lobes. It is almost an impossible job to untangle the entire story. She had, of course, Hodgkin's disease. That had been proved at the original biopsy, and she still showed active characteristic Hodgkin's involvement of many lymph nodes at the time of autopsy. Even at the time of death the liver and spleen were free. The lungs contained a great many nodules that were clearly due to Hodgkin's disease. In addition, however, there were some other things. For instance, there was an ordinary terminal bronchopneumonia, undoubtedly infectious in origin, not extensive, but enough to complicate the picture. There were still some cavities at the time of autopsy. These cavities showed nothing to suggest tuberculosis. I should also be inclined to say that they showed nothing to suggest infection, although I think that is difficult to rule out. One of the most striking features was the right upper lobe which was completely lacking in air and was of a uniform leathery consistence. I think the degree of dense fibrous consolidation in the upper lobe is not indicated adequately in any of the films. It had shrunken enough so that the apparent apex of the lung consisted actually of the apex of the lower lobe. Aerated lower-lobe tissue lay behind the upper lobe at all points, so that in the x-rays we get the appearance of at least some air in the apex of the lung, whereas there actually was none in the upper lobe.

Microscopic examination showed solid fibrosis of this entire lobe with extremely dense collagen and just an occasional remnant of an alveolus lined with cuboidal epithelium. Throughout this fibrous mass, however, one could still recognize persistence of alveolar walls. The elastic tissue had not been destroyed, and there was an alveolar pattern that could be brought out with the elastic-tissue stain but which was quite invisible with the hematoxylin and eosin stain. Where we found recognizable Hodgkin's involvement of the lung in this case, there was always complete destruction of the lung architecture. In the upper lobe there was fibrous obliteration of all the air sacs but the architecture was not obliterated. Either this was once Hodgkin's disease and all the Hodgkin's cells were killed or sterilized by x-ray so we could no longer recognize them, or we must assume that this fibrosis of the entire lobe was due to something else. I can only guess what that something else might be. The largest mass of nodes was in the lower right neck and was very resistant to therapy. She had a great many treatments to the right side of the neck, and many treatments to the mediastinum and chest. Therefore there was a possibility of a good deal of cross-firing, and much of the radiation that she had may have accumulated in this one area. The experimental production of x-ray pneumonitis has never been carried to such an extent as to produce anything like this picture. I cannot say that it has ever been proved that radiation pneumonitis can consolidate a lung to this extent, but I think it is more likely that the changes were produced in that way than that they were a part of the Hodgkin's involvement.

Dr. Maurice Fremont-Smith: What would be the effect of long-standing atelectasis? Do you get a picture comparable to that?

Dr. Mallory: I have never seen such a picture from pure atelectasis alone. The architecture is still further complicated by the fact that there is very extensive obliteration of the blood vessels throughout the area. This is unusual in organized pneumonias. There is fibrous plugging of bronchi as well as alveoli. There is in some places in the lung, but not in this right upper lobe,—which is most puzzling,—actual tumor thrombosis of blood vessels by the Hodgkin's disease thus accounting for small areas of infarction. However, infarction always destroys the lung pattern so that we can exclude it so far as the upper lobe is concerned. The walls of the various cavities again showed fibrosis and no recognizable Hodgkin's disease.

A Physician: Did the Hodgkin's disease invade the bronchi?

Dr. Mallory: It had grown around the bronchi in many places, but so far as we could make out had not invaded them, certainly not the larger ones.

Dr. Alfred Kranes: Is it not unusual to have radiation fibrosis confined to one lobe?

Dr. Mallory: There are many spots of a similar process scattered throughout the other lobes. These can apparently be distinguished from the Hodgkin's disease. All the other foci are relatively small compared with this one major involvement in the right upper lobe.

CASE 26242

Presentation of Case

A sixty-four-year-old man was admitted to the hospital because of mental disorientation with chills and fever.

Without apparent cause, approximately seven days before admission, the patient developed chills and a fever of 103°F., followed by a profuse sweat. A physician was called who prescribed "pills" and ordered the patient to remain in bed. However, his temperature remained at 100.6°F. and he continued to have "chilly sensations." Five days before admission he arose from bed still feeling chilly, but otherwise fairly well. The following day he went to work as usual, but that evening he "shook all over." On the third and second days before entry he remained at home, but out of bed, saying that he felt fairly well; but on the evening of the second day before entry, he again felt very chilly and afterward became warm. He became overtalkative and seemed unreasonable and somewhat confused. His physician was called, and the temperature was reported as having been 105°F. The confusion persisted and increased somewhat on the day before admission and the temperature remained at 103°F. all day. A pill prescribed by his doctor was vomited. Communication with the patient became somewhat difficult because of his confusion. Nevertheless his relatives believed that he had experienced headaches for some twenty-four hours before admission. Because of his symptoms he was admitted for study.

The past, marital and family histories were non-contributory.

Physical examination revealed a comatose, well-nourished man with shallow, slow, stertorous respirations. The skin was warm, clear and dry. The tongue was held in the mouth and appeared rough, moist and moderately coated. The throat was injected but without an exudate. Examination of the lungs was unsatisfactory because of shallow respirations. There was dullness at the bases posteriorly, up to the level of the ninth or tenth thoracic rib on each side. There were no definite signs of consolidation. The heart was described as normal. Examination of the abdomen was negative. There were varicose veins in the lower legs. Before admission the patient had been given morphine, and it was thought that part of the narcosis on entry was due to this.

The temperature was 103°F., the pulse 75, and the respirations 24.

A neurological examination, performed on the third hospital day, revealed the following findings: The patient was in semistupor, from which he could be aroused without difficulty. He replied to questions with single words and at times apparently had considerable difficulty in finding a word. He named most familiar objects correctly, but failed with a pencil. Co-operation was not very good. The fundi were not definitely abnormal. The temporal margins of the nerve heads were sharp, and the nasal margins only slightly hazy. The visual fields were full. The pupils were normal. The external ocular movements were normal, and there was no nystagmus. There was a questionable right facial weakness when pressure was applied to the eyeballs. The right handgrip was weaker than the left. The tendon reflexes were a shade more active on the right. The abdominal reflexes on the right were absent; on the left, positive. The neck was rigid. The plantar responses were normal. There was no tenderness over the sinuses or mastoids.

Examination of the blood showed a red-cell count of 3,400,000 with 11.1 gm. hemoglobin (photoelectric-cell technic), and a white-cell count of 35,000 with 94 per cent polymorphonuclears. The platelets were increased. Examination of the urine showed + to +++ albumin. The sediment on a few occasions showed from 1 to 5 red blood cells per high-power field. These occasional findings of hematuria were noted throughout his hospital stay. The blood Hinton test was negative. The serum nonprotein nitrogen varied from 25 to 43 mg. per 100 cc., but was usually normal. A lumbar puncture revealed a spinal fluid which showed an initial pressure of 400 mm. of water with a white-cell count of 3600 with 75 per cent polymorphonuclears, a total protein of 315 mg. per 100 cc., a sugar test of 19 mg. per 100 cc., chlorides of 639 mg. per 100 cc. and a gold-sol test of 4455556541. Culture and smear of the spinal fluid were negative for pathogenic bacteria.

Roentgenograms of the chest and mastoid regions were negative. The left antrum and frontal sinuses were slightly diminished in radiance. The superior wall of the left frontal sinus was hazy in outline and there was definite mottling in the frontal bone just above it. The appearance was suggestive of osteomyelitis, but further films did not confirm this finding.

A Type 29 pneumococcus was cultured from the sputum and blood. He was given sulfapyridine by mouth until the blood level reached as high as 16.1 mg. per 100 cc., but the levels averaged around 6 to 10 mg. He responded poorly to this therapy, however, so it was augmented with Type

29 antipneumococcus rabbit serum, in amounts equaling some 140,000 units. In spite of this and frequent transfusions, fluid parenterally and orally, adequate sedation and general nursing care, the disease continued to run a stormy course. The physical and neurological examinations remained essentially the same throughout his hospital stay, except that at one time a faint systolic murmur was heard over the precordium, but this had occurred at a time when there was a high fever. Microscopic hematuria persisted, and the urinary sediment contained pyridine crystals. No stabs of pain were complained of, and no petechiae or clubbing of the fingers was noted. The clinical picture, rather, was focused entirely on the central nervous system where there were never any localizing neurological signs.

The patient remained in the hospital for twenty-nine days, during which time his temperature spiked from 98 to 106°F. and the pulse and respirations were likewise irregular. The antibody content of the blood against Type 29 pneumococcus was found to be high. Type 29 pneumococci were agglutinated by serum in dilutions up to 1:64. Because of the failure of all therapy, artificial fever treatment was attempted for a period of a few hours, but to no avail. Repeat lumbar punctures showed essentially normal pressures with high cell counts, proteins ranging around 240 mg. per 100 cc., sugars around 20 mg. per 100 cc., and chlorides about 595 mg. per 100 cc. The spinal fluid contained neither agglutinins nor precipitins against Type 29 pneumococci. Accordingly, the Swift-Ellis type of treatment was attempted, with the introduction of a few centimeters of the patient's serum into the spinal canal, but this proved of no avail. During the last ten days of the patient's life he ran a spiking temperature, ranging daily from 99 to 104°F., with corresponding swings in pulse and respirations from 100 to 130 and 30 to 35, respectively. The patient gradually grew weaker and less responsive and then suddenly, without warning, died on the twenty-ninth hospital day or the thirty-sixth day of his illness.

Differential Diagnosis

Dr. Augustus S. Rose: The laboratory studies in this case delimit our problem. It is clearly indicated that we are dealing with a severe infectious process due to Type 29 pneumococcus. The clinical features suggest a meningitis, but as I will point out there are indications that the meningitis was secondary rather than primary and was not the actual cause of death.

If I might briefly review the important features of the history, the patient was a sixty-four-year-old man who suddenly without warning or apparent cause began to have chills and fever but who for five days was otherwise reasonably well. In fact on the fifth day he went to his work. The day before that he was up all day. Then suddenly, two days prior to admission, he became confused and overtalkative, and then gradually became semicomatose. When he entered the hospital we find that he had fever, a relatively slow pulse, stertorous respirations and stiff neck — signs which strongly suggest increased intracranial pressure and meningeal infection. This was later confirmed by lumbar puncture. The neurological examination indicated the possibility of changes in the left cerebral cortex or hemisphere. There was a questionable right facial weakness. The reflexes were slightly more active on the right side than they were on the left. The abdominal reflexes were absent on the right and he had some difficulty in choosing words. Any one of these findings alone would be difficult to interpret; but the fact that they all occurred together points definitely to some sort of localized abnormality in the left hemisphere. With the finding of cells in the spinal fluid and a sugar of 19 mg. per 100 cc. we are in a position to say that the patient had a bacterial meningitis, in spite of the negative culture from the spinal fluid. The question arises, Where did this meningitis come from? I think we are safe in assuming that it was due to the pneumococcus. Pneumococci usually enter the meninges from two sources: by direct extension from the paranasal sinuses or mastoid, or by way of the blood stream. The history in this case points to the blood stream as the probable source, but x-ray films suggested osteomyelitis of the left frontal sinus. Pneumococcal meningitis is a severe and often an overwhelming infection, and I do not believe that the first four days of this man's illness are consistent with that diagnosis. It is more likely that the meningitis developed two days before admission when his condition suddenly changed.

May we see the x-ray films?

Dr. Richard Schatzki: The x-ray evidence boils down to the appearance of the frontal sinuses. The other sinuses are fairly clear though there may be some chronic disease in one antrum. The left frontal sinus is different from the right. The wall is preserved but is less distinct than the one on the right side. These films were taken six days apart. The adjacent portion of the left frontal bone shows localized decalcification. How long had he been ill?

DR. ROSE: His symptoms began approximately one week prior to the time when the first x-ray film was taken.

DR. SCHATZKI: These questionable areas are sharply defined, more so than one would expect from osteomyelitis of one week's duration. I think one can exclude osteomyelitis of six days' duration. I do not see any definite pus in the sinus. I think it could be an osteomyelitis of, let us say, three weeks' duration.

DR. ROSE: The report indicates that the second films did not confirm the findings of the first.

DR. SCHATZKI: I think the examiner changed his mind, because the films are practically the same.

DR. F. DENNETTE ADAMS: Was there a chest plate?

DR. SCHATZKI: It does not show anything abnormal.

DR. ROSE: We are left somewhat in the air, having x-ray evidence that he possibly had a frontal sinusitis that might be of longer duration than his present illness although the early part of his illness hardly suggests this diagnosis. Certainly our record gives no history which leads us to suspect an acute frontal sinusitis. There were present none of the signs of a sinusitis or an osteomyelitis such as are usually found when extension of infection to the meninges occurs, for example, swelling or tenderness. So, I take the point of view that, if he had a sinusitis, it was probably of no significance in the development of his meningitis, unless it served as a possible source of the blood-stream infection. We are left, therefore, with the blood stream as the probable origin of his meningitis. The entire illness will be explained, it seems to me, if we can interpret the first five days of his illness. The history of chills and fever is consistent with a septicemia or at least a bacteremia, which we know was present shortly after admission.

We must now consider the possible sources of the pneumococcal bacteremia. We first turn to the respiratory tract and again find no evidence in the history. He had had no respiratory infection, complained of no sore throat or pain in the chest. The x-ray films of the lungs were negative, and although the throat was injected, apparently this was not due to a real pharyngitis. Nevertheless, the sputum contained pneumococci. We have mention of the veins of the leg as a possible focus, but we are told that there was no evidence of infection in them. We must, therefore, consider the heart as the possible source. Indeed, the entire illness can best be explained by the diagnosis of pneumococcal endocarditis, even though it began without evidence of an infectious focus. For five days he had repeated episodes of chills and fever. He then suddenly became confused and semicomatose and showed signs of meningitis and of a questionable localized lesion in the left cerebral hemisphere. The illness was terminated after a protracted but steady downhill course with a picket-fence temperature curve and in spite of adequate treatment. The laboratory findings showed an anemia of moderate grade and red blood cells in the urine on a number of occasions. The physical examination, however, does not offer much support. There were no petechiae. The spleen was not enlarged, and the finding of a systolic murmur on one occasion was modified by the statement that it was heard at a time when the temperature was elevated. Nevertheless, in the absence of any other demonstrable focus, the clinical course of the disease is strongly in favor of this diagnosis.

Before considering this as the only diagnosis, we ought to consider the possibility of a brain abscess which existed prior to the development of his symptoms, with rupture of the abscess producing the sudden onset of meningitis and subsequent infection of the blood stream and a continuous downhill course. I believe that the evidence is against a brain abscess that developed either before the onset of his present illness or during it. The fundi were normal, indicating that he did not have chronic increased pressure, although the first lumbar puncture showed an elevation of pressure. Furthermore, repeated tappings showed that the pressure subsequently remained low. This would not be expected if an abscess was present. In addition, the neurologic signs did not change significantly, as would be the case in an expanding lesion.

I am not sufficiently informed to discuss the therapy administered in this case except to say that a sulfapyridine level in the blood of 6 to 10 mm. is a level which is capable of producing a satisfactory therapeutic response. I do not know why fever therapy was used and I am puzzled by the use of the term "Swift-Ellis treatment," by which is usually meant the injection of neoarsphenamin intravenously and the subsequent injection of the patient's arsphenamized serum intrathecally. Did they use neoarsphenamin?

DR. TRACY B. MALLORY: I do not believe any neoarsphenamin was given. They merely injected his own serum into the spinal canal, in order to produce a higher concentration of antibodies in the subarachnoid space.

DR. ROSE: In summary, therefore, I believe the evidence points to the diagnosis of pneumococcal bacteremia with secondary pneumococcal meningitis and possibly septic cerebral infarct and pneumococcal endocarditis.

DR. CHARLES L. SHORT: I saw this case for only one purpose and that was to give fever therapy. The reason for this rested on some experiments showing that pneumococci in vitro may be more susceptible to sulfapyridine if the temperature is raised. So, all other measures having apparently failed, this patient was given fever therapy with radiant heat and his temperature kept above 103°F. for about four hours. This principle of treatment is not new. It has been used in the treatment of syphilis, combining chemotherapy with fever therapy, and also in the treatment of gonorrhea. As you see, there was apparently no beneficial effect from the fever therapy.

To answer Dr. Rose's comment, the patient, it is true, was having fever all along but if you examine the chart you can see that he was running a low fever with occasional spikes, but only after the fever therapy did he go into the period of intermittent high pyrexia.

DR. CHAMP LYONS: We did a great deal of laboratory work which in retrospect is interesting. In the first place, he had a negative spinal-fluid culture on entry with a positive blood culture. That should have been of a great deal of significance in the light of the subsequent diagnosis of endocarditis, because a true spreading leptomeningitis should give positive cultures in the spinal fluid. On entry he had no agglutinins in the blood or spinal fluid. With full-blown endocarditis we are accustomed to find a maximal concentration of agglutinins in the blood serum. Dr. Kubik and I talked over the question of endocarditis at that time, but there was no supporting clinical evidence. I believed that endocarditis could be fairly well excluded and Dr. Kubik also thought that it was unlikely. After we gave him immune serum, the serum agglutinin level came up to 1:12, but instead of dropping, it progressively rose during the subsequent hospitalization to a concentration of 1:64. That is an extremely high agglutinin titer and one which I believe should be diagnostic of endocarditis. He had negative chest signs, and we were never able to demonstrate any pulmonary infarction which one might have expected to find had the intravascular sepsis been a thrombophlebitis rather than an endocarditis. The subsequent blood cultures were negative by the routine method and in dilutions, but there was one experiment which was rather interesting. The question of sulfapyridine-fastness of this organism came up. We took his blood containing pyridine in a known level and a normal blood with a similar amount of pyridine and did a bactericidal experiment: the normal blood killed the pneumococcus perfectly well, although there were no agglutinins in the serum, whereas the patient's blood contained agglutinins but failed to kill the organism. We have as yet no explanation for that. It may be that the blood contained some pneumococci which we were unable to grow because of the concentration of the pyridine. But when we intensified the bacterial implantation by adding bacteria to the blood we increased the size of the inoculum sufficiently to overcome the bacteriostatic effect of the pyridine.

I should like to point out the fact that this method of using immune serum intrathecally is hazardous. We believe it is in general a bad principle in the treatment of meningitis. Sufficient meningeal irritation may occur to permit further abscess formation, hence there may not be so many successful recoveries if serum is used intrathecally. I believe from these studies that we have followed this patient from the onset of an endocarditis through to its fatal termination.

DR. CHARLES S. KUBIK: It might be of interest that there were 175 red cells in the first spinal fluid, 75 in the second two days later and again in the third fluid five days after that, but none subsequently. In the other cases of meningitis complicating bacterial endocarditis there have usually been some red cells, often a larger number than in this case. The combination of red cells in a purulent fluid, and particularly a xanthochromic purulent fluid, while not diagnostic, should lead one to think of subacute bacterial endocarditis. As Dr. Lyons has remarked we considered that as a possibility when the patient was first admitted but did not give it enough consideration later.

CLINICAL DIAGNOSES

Bacteremia (Type 29 pneumococcus).
Pneumococcal meningitis.
Multiple meningeal abscesses?

DR. ROSE'S DIAGNOSES

Pneumococcal bacteremia.
Pneumococcal meningitis (secondary).
Septic cerebral infarction?
Pneumococcal endocarditis?
Chronic frontal sinusitis?

ANATOMICAL DIAGNOSES

Bacterial endocarditis, acute, Type 29 pneumococcus.
Pneumococcal meningitis, embolic.

Infarcts of spleen and kidneys.

Exostosis of orbital plate of frontal bone.

Pathological Discussion

Dr. Mallory: The autopsy did show bacterial endocarditis. There were very large vegetations —1 to 2 cm. in diameter—on the mitral valve. There was no evidence of any preceding rheumatic involvement of the valve, but we know that with pneumococcal endocarditis such precedent valvular deformity is not necessary. There were emboli and consequent infarction in the spleen and kidneys. In the brain there were no gross infarcts, but there was a fairly diffuse meningitis. Microscopically small areas of partial infarction were noted. The frontal sinuses showed no infection, but there was a unilateral hyperostosis behind the left one which undoubtedly accounts for the unusual x-ray picture.

Dr. Adams: How often do you see pneumococcal endocarditis arise out of a clear sky?

Dr. Mallory: It is not very common but it does happen.

The New England
Journal of Medicine

Formerly the
Boston Medical and Surgical Journal
Established in 1828

Owned by the Massachusetts Medical Society and Published under the Jurisdiction of the Committee on Publications

Official Organ of
The Massachusetts Medical Society
The New Hampshire Medical Society
The Vermont State Medical Society

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Subscription Terms: $6.00 per year in advance, postage paid, for the United States; Canada, $7.04 per year; $8.52 per year for all foreign countries belonging to the Postal Union.

Material for early publication should be received not later than noon on Saturday.

The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston, Massachusetts.

PROLONGED RESIDENCIES: THEIR EFFECT ON MEDICAL EDUCATION

During the last twenty years there has been an evident tendency toward the prolongation of the periods of medical internship and residency. With the development of the boards of certification in the specialties this has been accelerated, and now that internal medicine and general surgery are included, it has become a problem of major importance to the entire profession. Schedules of four, five and even six years have been recommended or put into effect. As yet, however, little consideration has been given to the ways in which such a radical shift will affect medical education, hospitals and the young physicians who must go through this prolonged and rigorous training, and finally the practice of medicine. The following paragraphs deal with the first of these problems, and the others will be discussed in subsequent issues of the *Journal*.

There are two phases of medical education, each characterized by emphasis on a particular educational method. One, which may be termed the academic, is devoted to the accumulation of knowledge of the fundamental sciences on which medicine is founded — the biology of man; the second consists of training in the application of these sciences to clinical practice and of familiarization with the technics involved. The former is appropriately provided by an academic institution; the latter can best be acquired by an apprentice system that involves gradually increasing responsibility under adequate supervision — in present-day terms, an internship or residency. On the appropriate application of these two educational methods and on a proper balance between them depends the success of medical education.

In this country the emphasis has swung pendulum-like from one to the other. The apprenticeships of the Colonial Era and the early years of the Republic gave way, with the founding of medical schools, to a period of unalleviated didacticism in the middle portion of the last century. The reintroduction of bedside teaching in the rapidly growing charity hospitals started a trend in the reverse direction, which developed steadily into the clinical clerkships and intern systems of the first third of this century. To-day, with internship and residency programs stretching over periods of four to six years, apprenticeship dominates medical education to an even higher degree. But since it is in hospitals that this apprenticeship must be served now and in the future, one may reasonably ask, How many hospitals possess staffs capable of offering a genuinely educational program over so extensive a period? Dean Rappleye,* of Columbia, after prolonged study of the situation, is justifiably skeptical of their ability and, almost alone among the administrators of the large medical schools, calls for close co-operation between schools and hospitals in the development of such programs.

The great majority of medical schools have stood decorously aloof or have more or less openly im-

*Rappleye, W. C.: The challenge to medical education. *J. A. Am. M. Coll.* 15:1-8, 1940.

plied that this phase of medical education is no concern of theirs. Yet it is from those who are trained by this apprenticeship that their clinical faculties will soon be recruited. Far from evincing concern over the diminishing proportion of medical education that they control they have treated with almost complacent neglect the recommendation of the Advisory Board of Medical Specialties, namely, that all candidates return after a period of internship to a further year of work at the medical schools in one or more of the basic sciences.

Is the preclinical training in the present medical schools so adequate that such a year would be superfluous? Does anything more fundamental than custom and administrative convenience demand that all academic work should precede the first contact with a sick human being? Experience in teaching a basic science not only in the preclinical period but also to fourth-year men and graduate students strongly indicates that the answer to both questions should be, No. Furthermore, in many other fields of education, experiments in the alternation of periods of academic instruction with those of practical experience have proved highly successful, and the avidity with which graduate students seize on scientific material which can be correlated with clinical experience indicates that the method is pedagogically sound.

Surely the time is ripe for a re-evaluation of all medical education. In view of the appalling number of years to which it has been prolonged this can hardly be too extensive. The study should include the premedical years, with a view to the admission of students to the medical schools at an earlier age. It should consider the feasibility of telescoping at least one of the clinical years into the basic internship, and it should seriously consider the advisability of a return to academic work after internship for those desiring advanced training.

MILK: GOOD, BETTER, BEST

Considerable water has gone over the dam in the last two or three years in relation to the milk industry; none of it has gone into the milk, either chemically or economically. Milk standards have tended steadily to improve; milk profits have continued to be precarious, with relatively high costs of production and an uncertain and unsatisfactory volume of consumption. Government, union and farmer-labor price-fixing, Mayor LaGuardia's public proclamation urging substitution of Grade B for Grade A milk to combat the cost of the latter, and the blast at the business in the November issue of *Fortune,* under the title "Let 'Em Drink Grade A," have not served to smooth the path of an essential industry.

The main theses of the broadside in *Fortune* were: that consumers do not use so much milk as they should because of high price; that the price of milk is too high and could be reduced; that milk can be sold through stores at four cents a quart less than through home-delivery; that organized labor and organized farmers have in many markets arbitrarily raised wages and farm prices to uneconomic levels; and that the milk distributor has helped to support this policy in order to keep consumer prices at high levels. Dr. Edward Fisher Brown, writing for the Milk Research Council, refutes these statements: price of milk is not arbitrarily set by money-grabbing milk companies, but is determined by a number of relatively fixed charges — a price paid to the farmer that is set in many important markets by the federal or state government, a wage scale negotiated with labor unions, the cost of supplies and taxes. Retail price is raised but little by company profits; this increase was shown by an audit in New York State not to exceed three-eighths of a cent a quart. Furthermore, Dr. Brown points out that high consumer prices diminish consumption, and that profit comes not with decreased but with increased consumption; hence the main interest of dealers is to cut costs, thus increasing the sale of milk.

The policy of milk grading is a sound one, excluding the ballyhoo that has been raised about certain fancy "premium" milks. From a medical point of view there should be some guarantee that all grades of milk are safe. This is ensured if minimum standards are invoked as in Boston, where market milk may have no more than 400,000

bacteria raw, and, of recent date, no more than 20,000 pasteurized, and can be sold only pasteurized. Grade A milk may now have only 50,000 bacteria raw, and 5000 pasteurized, and certified milk, produced under the direction of the Boston Medical Milk Commission, may have only 5000 bacteria in its raw state and only 100 after pasteurization. Add a price difference of only four or five cents a quart between certified and Grade A milk, and the choice of the former as the milk par excellence seems justified.

Even assuming that all grades of milk are safe for the consumer, the marketing of better grades of milk with fewer bacteria, more calories, greater freshness and a higher vitamin and mineral content is logical, sound and ethical business. No reason exists for abolishing porterhouse steak simply because some consumers can afford only hamburg. In this direction lies totalitarianism.

MEDICAL EPONYM

Cardarelli - Oliver Sign

"Sulla pulsazione del tubo laringotracheale, come segno di certi aneurismi dell'arco aortico [Pulsation of the laryngotracheal tube as a sign of certain aneurysms of the aortic arch]" was described by Professor Antonio Cardarelli (1831 - 1927) in *Il movimento medico-chirurgico* (1: 223 - 229, 1872). A portion of the translation follows:

> On observing the anterior aspect of the neck, I noted that the whole laryngotracheal tube was shaken by a rhythmic and easily perceptible impulse, and this was all the more noteworthy and important since the pulsation of both carotid arteries was feeble. . . . This pulsation of the laryngotracheal tube was much more notable in another case . . . [in which] it was not only perceptible on laying the fingers on either side of the tube, but was perceptible on inspection of the thyroid gland, which with every arterial pulsation was carried toward the right.

Six years later, the following letter from Surgeon-Major W. S. Oliver, dated September 13, 1878, was printed in the *Lancet* (2: 406, 1878), under the title "Physical Diagnosis of Thoracic Aneurism."

> As the diagnosis of thoracic aneurism of the aorta is often difficult and obscure, notwithstanding the various physical means we have now at our disposal for detecting it, I am desirous of mentioning a method of examination which has afforded me material assistance in diagnosing this disease (or even simple dilatation of the vessel), when it occurs, as is most generally the case, either in the ascending or the first part of the transverse portion of the arch.
>
> The process is as follows: place the patient in the erect position, and direct him to close his mouth and elevate his chin to the fullest extent, then grasp the cricoid cartilage between the finger and thumb, and use gentle upward pressure on it, when, if dilatation or aneurism exists, the pulsation of the aorta will be distinctly felt transmitted through the trachea to the hand. The act of examination will increase laryngeal distress should this accompany the disease.
>
> R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

SECTION OF OBSTETRICS AND GYNECOLOGY*

Raymond S. Titus, M.D., *Secretary*
330 Dartmouth Street
Boston

Pyelitis of Pregnancy Treated with Sulfanilamide

Mrs. D. J. C., a twenty-eight-year-old primipara, thirty-six weeks pregnant, was seen at home on March 20, 1939, because of severe back pain, chilliness and general malaise. On examination the temperature was found to be 100.6°F., and the pulse 115. There was marked bilateral costovertebral tenderness. A probable diagnosis of acute pyelitis was made, and the patient was sent to the hospital.

The patient's past history was essentially negative. Catamenia began at fourteen, were regular with a twenty-eight-day cycle and lasted four days without pain. The last period was July 16, 1938, making confinement due April 23.

The patient was first seen on September 18, 1938, at which time a physical examination was essentially negative except for an enlarged uterus which was consistent with the duration of the amenorrhea. The urine was negative. The hemoglobin was 70 per cent, and because of this, the patient was told to take 5 gr. of ferrous sulfate three times a day.

Except for some gastric disturbance, possibly due to the iron, the pregnancy progressed uneventfully until the date above mentioned. On admission to the hospital the white-cell count was found to be 15,000 and a catheter specimen of urine showed a large amount of pus. The hemoglobin was 52 per cent, and the red-cell count 3,030,000. She was started at once on 15 gr. of sulfanilamide four times a day, and a red-cell count and hemoglobin determination were made every other day.

On March 21 the temperature did not go above

*A series of selected case histories by members of the section will be published weekly. Comments and questions by subscribers are solicited and will be discussed by members of the section.

99.2°F., and thereafter was normal. She was discharged on March 25, completely relieved symptomatically but still showing pus cells in the urine. Urine culture had shown a colon-bacillus infection. Sulfanilamide was discontinued when she was discharged from the hospital.

The patient continued to show pus in the urine but remained symptomatically well and afebrile until April 15, when she had a recurrence of back pain with a temperature of 102°F. and was readmitted to the hospital. She was again started on 15 gr. of sulfanilamide four times a day. On April 16 the temperature was 101.2°F.; on April 17 it was normal. Vaginal examination showed the head engaged in the pelvis, the cervix partly taken up and the os almost admitting two fingers. In view of the proximity to term and the state of the cervix, it was decided that induction of labor was the best treatment. This was done, and the patient was delivered of a 7-pound, 5-ounce, infant in good condition. In view of the urinary infection, it was thought best to forestall any urinary retention by immediately putting the patient on constant drainage. Sulfanilamide was omitted following delivery. The puerperium was entirely afebrile. The catheter was removed on the fourth day, following which the patient voided normally. The patient was discharged well on the fourteenth day. Examination of the urine a week later showed no pus.

Comment. Sulfanilamide in the treatment of pyelitis during pregnancy has had such success that it is probable that its use will become routine. The results in this case in which no renal lavage was undertaken would lead to the belief that lavage of the kidney is perhaps entirely unnecessary. It is much too soon to draw any conclusions as to whether the drug prevents the kidney damage that was seen so often following recurrent attacks of pyelitis.

VETERANS' INFORMATION ON DEATH CERTIFICATES

The attention of all fellows is invited to Sections 9 and 10 of Chapter 46 of the General Laws which require that the status of the deceased as a veteran must be determined by the physician signing the death certificate. Failure to supply this information renders the physician liable to a fine.

There has been some misunderstanding on the part of local authorities in this connection, and in many cases the entire death certificate, with the exception of the medical certificate, is filled out by the undertaker or other persons.

It is understood that the Secretary of State is preparing a new form to correct this misunderstanding but, in the meantime, great care should be used by the physician in checking this item.

ALEXANDER S. BEGG, M.D., *Secretary.*

DEATH

STANLEY — JOSIAH M. STANLEY, M.D., of Northboro, died June 4. He was in his eighty-first year.

Born in Methuen, he attended Yale University and received his degree from the New York University Medical College in 1884. After serving his internship at Bellevue Hospital, New York City, he took a postgraduate course at Harvard Medical School.

Dr. Stanley was town and school physician for twenty-five years in Northboro. He was a fellow of the Massachusetts Medical Society and the American Medical Association.

His widow survives him.

Erratum. Through an error, it was announced in the June 6 issue of the *Journal* that Dr. George G. Sears died on May 27; the correct date is May 28.

MISCELLANY

RÉSUMÉ OF COMMUNICABLE DISEASES IN MASSACHUSETTS FOR APRIL, 1940

DISEASES	APRIL 1940	APRIL 1939	FIVE-YEAR AVERAGE*
Anterior poliomyelitis	0	1	0
Chicken pox	1286	719	1098
Diphtheria	11	9	17
Dog bite	937	938	976
Dysentery, bacillary	24	7	5
German measles	55	96	1939
Gonorrhea	368	355	440
Lobar pneumonia	522	607	577
Measles	2464	4063	3242
Meningococcus meningitis	5	4	16
Mumps	756	708	1052
Paratyphoid B fever	3	0	8
Scarlet fever	756	767	1165
Syphilis	479	423	502
Tuberculosis, pulmonary	206	224	319
Tuberculosis, other forms	20	30	34
Typhoid fever	10	8	6
Undulant fever	4	2	3
Whooping cough	625	798	705

*Based on figures for preceding five years.

RARE DISEASES

Diphtheria was reported from: Fall River, 3; Fitchburg, 1; Lawrence, 1; Northbridge, 1; Somerville, 1; Watertown, 1; Wrentham, 3; total, 11.

Dysentery, bacillary, was reported from: Arlington, 3; Belchertown, 7; Belmont, 1; Boston, 1; Brookline, 2; Greenfield, 1; Lowell, 8; West Boylston, 1; total, 24.

Malaria was reported from: Cambridge, 3; total, 3.

Meningococcus meningitis was reported from: Brockton, 2; Framingham, 1; Orange, 1; Quincy, 1; total, 5.

Paratyphoid B fever was reported from: Beverly, 1; Dedham, 1; Milton, 1; total, 3.

Pellagra was reported from: Boston, 1; Winchester, 1; total, 2.

Pfeiffer bacillus meningitis was reported from: Charlton, 1; total, 1.

Septic sore throat was reported from: Belmont, 1; Beverly, 1; Boston, 4; Brockton, 1; Cambridge, 4; Chicopee, 1; Fall River, 1; Georgetown, 1; Lexington, 1; Lynn, 1;

Malden, 3; Medford, 4; Melrose, 1; Milford, 1; Milton, 1; New Bedford, 1; Salisbury, 1; Somerville, 1; Waltham, 1; Wakefield, 1; West Springfield, 1; total, 32.

Tetanus was reported from: Fall River, 1; Worcester, 1; total, 2.

Trachoma was reported from: Watertown, 1; total, 1.

Trichinosis was reported from: Newton, 1; total, 1.

Typhoid fever was reported from: Framingham, 1; Somerset, 1; Somerville, 7; Worcester, 1; total, 10.

Undulant fever was reported from: Ashburnham, 1; Dedham, 1; West Springfield, 1; Worcester, 1; total, 4.

Typhoid fever had its highest April incidence since 1935. A focus in Somerville accounts for the major part of this increase.

Bacillary dysentery, primarily of the Sonne and Hiss-Y types, continues to be reported well above the five-year average.

The reported incidence of chicken pox is slightly above the five-year average.

German measles, measles, mumps and scarlet fever were reported well below the five-year average.

Gonorrhea, syphilis and meningococcus meningitis were reported at expected levels.

There was nothing remarkable in the reported incidences of anterior poliomyelitis, diphtheria, lobar pneumonia, tuberculosis, whooping cough and undulant fever.

NOTE

At the recent annual meeting of the American Laryngological Association, held at Harrison, New York, Dr. Gordon Berry, of Worcester, Massachusetts, was elected president and Dr. Charles T. Porter, of Boston, first vice-president.

CORRESPONDENCE

GUAJAKODYL

To the Editor: During the past two years I have received numerous requests from physicians throughout New England for information regarding the product Guajakodyl. These requests are based on the fact that the manufacturers of this product gave me a quantity to use in the Pulmonary Clinic at the Massachusetts General Hospital. I should like to state briefly the results of its use.

This material contains 0.05 gm. of guaiacol and 0.025 gm. of cacodylic acid per cubic centimeter of water. The total of approximately 500 cc. was given to a group of seven patients. The doses ranged from 1 to 4 cc. intramuscularly at intervals of one to three days. The largest amount to one patient was 138 cc. over a period of two months. Routine complete urine examinations were done frequently on all patients, and no difficulties were noted with the use of the product other than the complaint of transient dizziness which frequently followed the injections. No evidence of renal or skin irritation was noted. The patients all had bronchiectasis. There was no change in the course of the disease. The patients said that the material caused them no difficulty, and all stated that the sputum was thinner and that they were able to raise it more easily while they were taking the medicine. The patient receiving the large dosage had extensive disease with multiple cavities and foul sputum. The foulness was converted to a creosote odor, and both the patient and the family were convinced that the drug made things much more pleasant for all concerned. Guaiacol by mouth had caused a severe gastritis in this patient.

It seems that this product is harmless in the quantities used, and that it is a satisfactory expectorant and deodorant, particularly in a case with foul sputum. Through the manufacturers I have contacted a number of reliable physicians who have been using this product, and these doctors state that a total of approximately 5000 cc. of this material has been used by them without any ill-effects.

JOHN W. CASS, JR., M.D.

1101 Beacon Street,
Brookline, Massachusetts.

ARTICLES ACCEPTED BY THE COUNCIL ON PHARMACY AND CHEMISTRY, AMERICAN MEDICAL ASSOCIATION

To the Editor: In addition to the articles enumerated in our recent letter the following have been accepted:

McKesson and Robbins, Inc.
McKesson's Ascorbic Acid Tablets, 25 mg.

Shark Industries
Shark Liver Oil

Sharp and Dohme, Inc.
"Lyovac" Antivenin (Nearctic Crotalidae) Polyvalent

Smith, Kline and French Laboratories
Benzedrine Sulfate Ampules, 10 mg., 1 cc.

The Upjohn Company
Ampoules Sterile Solution Caffeine with Sodium Benzoate, 0.5 gm. (7½ gr.), 2 cc.
Hypodermic Tablets Caffeine with Sodium Benzoate, 0.065 gm. (1 gr.)

John Wyeth and Brother, Inc.
Thyroid Tablets

PAUL NICHOLAS LEECH, *Secretary.*

535 North Dearborn Street,
Chicago, Illinois.

REPORTS OF MEETINGS

HARVARD CHAPTER OF NU SIGMA NU

At the Harvard Medical School on February 29, the Harvard Chapter of Nu Sigma Nu presented Dr. D. D. Van Slyke, of the Rockefeller Institute, New York City.

The speaker recounted physiological studies of the kidney which originated from an attempt to explain the mechanisms that maintain the constancy of the urea clearance under conditions of varying blood concentration. In a normal man the kidneys excrete per minute the amount of urea contained in about 75 cc. of blood: the "urea clearance" is 75 cc. per minute. If the blood-urea concentration is doubled, the excretion rate doubles, so that the kidneys still clear 75 cc. of blood per minute.

In experiments with dogs in which the renal veins were made accessible by Rhoads's "explanting" in operation, it was found that this constancy of the clearance in the presence of changing blood-urea concentration is due to the fact that the kidneys regularly remove from the renal blood a constant fraction, approximately one twelfth, of the urea. This occurs whether the blood-urea concentration is high or low. Consequently, if the renal blood flow is constant, the urea clearance remains constant. Va-

riations in the clearance could be induced in dogs by varying their renal blood flow, but the fraction of urea removed remained the same. In man, if the kidneys, as in the dog, remove one twelfth of the urea from the renal blood, the average clearance of 75 cc. indicates a renal blood flow of 900 cc. per minute, and other data indicate that this is in fact about the rate of blood flow through human kidneys.

Under ordinary conditions, the urea clearance appears to vary in proportion to the renal blood flow. It falls when the renal blood falls, when, as in shock, blood is withdrawn from the peripheral circulation, or when, as in chronic nephritis, destruction of glomerular tissue cuts down the channels for renal blood flow. The clearance has been useful in following the progress of Bright's disease. When the urea clearance falls to 5 per cent of normal, and not until then, death in uremia is imminent. In acute nephritis the clearance may fall to 10 per cent of normal, and recovery still occur, if the clearance begins to rise within four months.

The extracted fraction of the urea in the renal blood does not appear, under all conditions, to remain constant at one twelfth. Smith and Goldring, estimating the renal blood flow in man from the Diodrast clearance, have found that under the influence of adrenalin and of certain other factors the clearance can undergo wide variations without variation of the renal blood flow. Under these conditions, the variations are due to changes in the extracted fraction. Smith and Goldring's explanation is that constriction and relaxation of the efferent glomerular arterioles occur under the influences mentioned, and thereby vary the blood pressure in the glomerular capillaries. As a result, parallel variations are caused in the proportion of plasma water which, according to the filtration-reabsorption theory, is filtered in the glomeruli. These variations in filtration compensate for changes in renal blood-flow rate, and leave the clearance constant.

The theory of renal excretion mentioned accords with all the known facts of renal physiology, and aids in their comprehension, it was asserted. It is based on work by Cushny, Richards, Marshall, Smith, Shannon and others. According to it, as the blood perfuses the kidneys part of the plasma water is filtered into the glomerular capsules. Richards and his colleagues have collected the filtrate from individual glomeruli of frogs' kidneys, and have shown by ultramicroanalyses that it is a true plasma filtrate, containing all the filterable substances of the plasma in the same concentrations as those in the plasma.

The proportion of plasma water filtered was made the object of study in the speaker's laboratory by observations on dogs with kidneys explanted by Rhoads. It was found to average 20 per cent of the entire plasma water. With this water is filtered 20 per cent of the urea, uric acid, sugar and so forth dissolved in the plasma.

As the filtrate passes down the tubules the greater part of the water, an average of about 98 per cent in man, is reabsorbed into the blood. This reabsorption is necessary, for the volume of the glomerular filtrate formed in twenty-four hours by a man is calculated to be about 150,000 cc. This much has to be filtered to remove waste products at a physiological rate, but the water must be taken back or man in a dry environment would be in continual danger of death from desiccation.

With the water some of the dissolved substances of the glomerular filtrate are partly or completely reabsorbed. They may be divided into three groups: substances, like glucose, that the body needs to retain completely, and that are completely reabsorbed so that none escape in the urine; substances like sodium chloride, of which a certain amount needs to be retained in order to maintain physiological composition of the body fluids — of these substances the renal tubules reabsorb what is needed, the excess passing into the urine; and substances that are merely excretory waste products, like urea and creatinine, and for which there is no physiological reason for reabsorbing. The tubules do not reabsorb these last substances actively, and in fact act as a barrier to their diffusion into the blood with the reabsorbed water. This barrier is not perfect, and some of the filtered urea and uric acid diffuse back, but the proportion is slight compared with that of the substances in the first two groups.

Dr. Van Slyke mentioned how the alkali reserve of the body is maintained by this process of selective reabsorption, The sodium bicarbonate that is filtered out in the glomeruli is almost completely reabsorbed in the tubules. Furthermore, ammonium bicarbonate is formed in the kidney and is apparently extruded into the proximal part of the tubule; then in the distal part a combined chemical and physiological reaction occurs whereby the ammonium bicarbonate combines with the sodium chloride filtered from the glomeruli, and sodium bicarbonate is reabsorbed while the ammonium chloride passes into the urine. The effect of this process is to replace blood sodium chloride with sodium bicarbonate. Simple reabsorption of filtered sodium bicarbonate, first mentioned, prevents loss of bicarbonate from the blood. But the replacement of sodium chloride by sodium bicarbonate through the above chain of events adds to the bicarbonate reserve of the body. Through this mechanism ammonia enables the body to restore its alkali reserve when it has been depleted by acidosis.

The speaker concluded that the filtration-reabsorption theory accords with what is known concerning the processes by which the kidneys prevent the escape of glucose into the urine, regulate the volume and electrolyte content of the body fluids, excrete waste products of metabolism and regulate the acid-base balance of the body.

NOTICES

ANNOUNCEMENTS

John Homans, M.D., announces the opening of an office at 311 Beacon Street, Boston.

Joseph H. Mezer, M.D., announces the removal of his office from 270 Commonwealth Avenue to 520 Beacon Street, Boston.

Robert J. Sherman, M.D., announces the opening of an office at Guild Square, Norwood.

SOUTH END MEDICAL CLUB

The next meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, June 18, at 12 o'clock noon. Dr. Paul D. White will speak on "The Doctor and His Heart."

Physicians are cordially invited to attend.

SOCIETY MEETINGS AND CONFERENCES

Calendar of Boston District for the Week Beginning Sunday, June 16

Tuesday, June 18

*12 m. The Doctor and His Heart. Dr. Paul D. White. South End Medical Club, headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston.

June 23–25 — Maine Medical Association. Annual meeting. Rangeley Lakes.

JUNE 25–27 — Medical Library Association. Page 862, issue of May 16.

JUNE 27 — Pentucket Association of Physicians. The Try-Angle, Groveland.

SEPTEMBER 2–6 — American Congress of Physical Therapy. Page 862, issue of May 16.

OCTOBER 8–11 — American Public Health Association. Page 655, issue of April 11.

OCTOBER 11, 12 — Pan-American Congress of Ophthalmology. Page 898, issue of May 23.

OCTOBER 14–25 — 1940 Graduate Fortnight of the New York Academy of Medicine. Page 938, issue of May 30.

OCTOBER 21 — American Board of Internal Medicine, Inc. Page 369, issue of February 29.

DISTRICT MEDICAL SOCIETY

MIDDLESEX NORTH

JULY 31.

OCTOBER 30.

BOOKS RECEIVED FOR REVIEW

The Endocrine Glands. Max A. Goldzieher. 916 pp. New York and London: D. Appleton-Century Co., Inc., 1939. $10.00.

A Textbook of Pathology. W. G. MacCallum. Seventh edition. 1302 pp. Philadelphia and London: W. B. Saunders Co., 1940. $10.00.

Clinical Heart Disease. Samuel A. Levine. Second edition. 495 pp. Philadelphia and London: W. B. Saunders Co., 1940. $6.00.

The Individual and His Society: The psychodynamics of primitive social organization. Abram Kardiner. 503 pp. New York: Columbia University Press, 1939. $3.50.

Your Marriage: A guide to happiness. Norman E. Himes. 434 pp. New York and Toronto: Farrar & Rinehart, Inc., 1940. $3.75.

Dental Roentgenology. LeRoy M. Ennis. Third edition. 398 pp. Philadelphia: Lea & Febiger, 1939. $6.50.

Chemistry and Medicine: Papers presented at the Fiftieth Anniversary of the Founding of the Medical School of the University of Minnesota. Edited by Maurice B. Visscher. 296 pp. Minneapolis: University of Minnesota Press, 1940. $4.50.

An Anatomical Analysis of Sports. Gertrude Hawley. 191 pp. New York: A. S. Barnes & Co., 1940. $3.00.

Physiological Optics. W. D. Zoethout. Third edition. 406 pp. Chicago: Professional Press, Inc., 1939. $5.00.

Periodontal Diseases: Diagnosis and treatment. Arthur H. Merritt. Second edition. 205 pp. New York: Macmillan Co., 1939. $3.50.

The Vasomotor System in Anoxia and Asphyxia. Ernst Gellhorn and Edward H. Lambert. 70 pp. Urbana, Illinois: University of Illinois Press, 1939. $1.00.

An Index of Treatment. By various writers. Edited by Robert Hutchison. Twelfth edition. 996 pp. Baltimore: Williams & Wilkins Co., 1940. $12.00.

An Atlas of the Commoner Skin Diseases. Henry C. G. Semon. Second edition. 272 pp. Baltimore: Williams & Wilkins Co., 1940. $12.00.

Cyclopropane Anesthesia. Benjamin H. Robbins. 175 pp. Baltimore: Williams & Wilkins Co., 1940. $3.00.

Asthma and the General Practitioner. James Adam. 157 pp. Baltimore: Williams & Wilkins Co., 1939. $2.00.

Psychiatry for Nurses. Louis J. Karnosh and Edith B. Gage. 327 pp. St. Louis: C. V. Mosby Co., 1940. $2.75.

A Synopsis of Surgery. Ernest W. H. Groves. Eleventh edition. 714 pp. Baltimore: Williams & Wilkins Co., 1940. $5.00.

Population: A problem for democracy. The Godkin Lectures, 1938. Gunnar Myrdal. 237 pp. Cambridge: Harvard University Press, 1940. $2.00.

Modern Medical Therapy in General Practice. Edited by David P. Barr. 3 vol. 3661 pp. Baltimore: Williams & Wilkins Co., 1940. $35.00.

The Way Life Begins: An introduction to sex education. Bertha C. Cady and Vernon M. Cady. 80 pp. New York: American Social Hygiene Association, 1939. $1.50; 50c paper cover.

Digest of Laws and Regulations: Relating to the prevention and control of syphilis and gonorrhea in the forty-eight states and the District of Columbia. Compiled under the direction of Bascom Johnson. 438 pp. New York: American Social Hygiene Association, 1940. $5.00.

Sulfanilamide, Sulfapyridine and Allied Compounds in Infections. Maurice A. Schnitker. Edited by Henry A. Christian. 72 pp. New York, London and Toronto: Oxford University Press, 1940. $1.50.

Operative Surgery. J. Shelton Horsley and Isaac A. Bigger. Fifth edition. 2 vol. 1567 pp. St. Louis: C. V. Mosby Co., 1940. $18.00.

Doctors in Shirt Sleeves: Musings on hobbies, meals, patients, sport and philosophy. Edited by Henry Bashford. 294 pp. New York: Veritas Press, 1940. $2.50.

Pediatrics and Pediatric Nursing. A. Graeme Mitchell, Echo K. Upham and Elgie M. Wallinger. 575 pp. Philadelphia and London: W. B. Saunders Co., 1939. $3.00.

Trends in Nursing History: Their relationship to world events. Elizabeth M. Jamieson and Mary Sewall. 570 pp. Philadelphia and London: W. B. Saunders Co., 1940. $3.00.

BOOK REVIEWS

The Electrocardiogram and X-Ray Configuration of the Heart. Arthur M. Master. 222 pp. Philadelphia: Lea & Febiger, 1939. $6.50.

Dr. Master has composed an atlas of electrocardiograms and x-ray pictures of the heart for beginners who have had their fundamental grounding in technic and principles. The volume may prove helpful even to those more skilled in cardiology since there are a number of points that the author emphasizes which are not kept constantly in mind, or concerning which there have been advances. For example, he calls attention to the fact that in a case of valvular heart disease the presence of high voltage without axis deviation usually indicates both left and right ventricular enlargement.

He explains the purpose of the book in the first two paragraphs of the preface as follows:

> Excluding arrhythmias, electrocardiography may be divided into two parts, the changes associated with muscle damage, acute or chronic, and those related to the configuration of the cardiac chambers. Examples of the first group are rheumatic carditis, myocardial infarction and fibrosis, lobar pneumonia, typhoid fever and acute nephritis. The second group includes factors such as age, body position, habitus, obesity, pregnancy, hypertension, valvular disease, congenital heart disease, pulmonary disease and deformities of the chest which alter the contour of the heart. The significance of the second group has been largely neglected, and this monograph has been written in the effort to correct this, since an appreciation of the dependence of the electrocardiogram on the size, shape and position of the heart is absolutely fundamental in the interpretation of the electrocardiogram.
>
> The need for such a book is indicated particularly at the present time, since electrocardiographic instruments are now obtainable at quite low prices and the

technique of taking the record has become very simple. As a result a large number of physicians are now taking and interpreting electrocardiograms without the study and application necessary for doing this properly.

The contents include, after a short introduction, a brief statement about the normal electrocardiogram. Illustrations follow showing the effect of age on the contour and size of the heart and on the electrocardiogram, beginning with the newborn and proceeding to extreme old age. Next there is an important section on the effect of change with body position and respiration, and the relation of the x-ray plate and electrocardiogram to body habitus. These illustrations are perhaps the most important in the book for they are most often wrongly interpreted. There follows a discussion of axis deviation and ventricular preponderance; first of the left side of the heart secondary to hypertension and aortic valvular disease, and second of the right side of the heart secondary, chiefly, to mitral stenosis. There is a presentation of the effect of combined valvular disease of the heart and of symmetrical enlargement due to other causes, and a section on congenital heart disease. The last five sections deal with auricular enlargement, Graves's disease, pericardial effusion, pulmonary disease (with the acute and chronic cor pulmonale) and deformities of the chest.

The most difficult part of the book and that section which is the least well presented concerns congenital heart disease. One may raise a question about the interpretation of several of the cases, particularly Cases 51, 53 and 56. One also misses in the discussion of thyroid disease the characteristic x-ray picture and electrocardiogram of well-marked myxedema. One may question the statement on page 96 that a slurring of the QRS group indicates myocardial involvement. Such slight slurring as is shown is consistent with marked enlargement of the heart, which may also account for increase in the width of QRS waves without the need of interpreting bundle-branch block. This latter point Dr. Master emphasizes, on page 108, as an important and relatively new point of view, which he states that he will present in a further publication. The statement on page 160 that, in the case of the tetralogy of Fallot, right-axis deviation is the result of the large right ventricle, whereas the increased amplitude of the QRS complex is probably caused by the enlarged left ventricle, is open to question, since in such cases the left ventricle is not enlarged and the increased amplitude of the QRS complexes is quite adequately explained by the very large right ventricle. There are two or three minor errors: on pages 28 and 29 left ventricular hypertrophy might be better expressed as left ventricular preponderance since the heart itself is stated to be normal, and on page 181 the word "restored" in the legend should be "absorbed."

One of the interesting aspects of the book is the inclusion of brief historical references. In the discussion of large P waves one might add on page 171 Samoiloff's name, since he contributed an important paper in 1909 on the large P waves of mitral stenosis.

There are two figures that are especially instructive in showing the evolution of the electrocardiogram: Figure 31, which shows the development of the hypertensive electrocardiogram, and Figure 38, which shows the development in both the electrocardiogram and roentgenogram of progressive enlargement of the left ventricle secondary to syphilitic aortic insufficiency.

The text of the book is clear and simple. The illustrations are clear cut and well arranged. The reviewer was at first disturbed by the fact that some of the x-ray pictures were in different positions, even upside down, but such pictures were so arranged to indicate the position in which the person was lying at the time, showing the effect of change in position.

The plan of this book is novel and brings together more extensively than has been done before the combination of roentgenographic and electrocardiographic patterns in structural defects of the heart.

A Symposium on Cancer. Given at an Institute on Cancer Conducted by the Medical School of the University of Wisconsin. 202 pp. Madison: University of Wisconsin Press, 1938. $3.00.

This group of addresses given at the Institute on Cancer conducted by the Medical School of the University of Wisconsin in 1936 gives a considerable amount of interesting information. The material presented was new and of interest at that time, but the field has naturally progressed considerably in the past three and a half years.

There are two articles on experimental tumor production by Kreyberg, an excellent review of the value of tissue cultures in the study of cancer by Lewis and addresses on a number of other fields of cancer research that are sound but somewhat ephemeral in their interest. There would be some disagreement with Macklin's interpretation of the familial incidence of cancer. Likewise, some would question Coutard's estimate that 15 to 20 per cent of all breast cancers are extremely radio-sensitive.

A Mirror for Surgeons: Selected readings in surgery. D'Arcy Power. 230 pp. Boston: Little, Brown & Co., 1939. $2.00.

By training, temperament and experience, Sir D'Arcy Power — the dean of the British surgical profession, so referred to by Dr. Francis R. Packard, who writes the "Introduction" — is peculiarly qualified to present to the medical profession essays containing brief biographical notes and extracts from some of the writings of twenty-two surgeons. Perhaps the most satisfying compensation offered to the reader by these selected readings in surgery is the opportunity of following the evolution of surgical thinking, beginning with the quaint English of John Arderne in the fourteenth century. The surgeons considered are as follows: Thomas Gale, Ambroise Paré, John Halle, William Clowes, Maister Peter Lowe, John Woodall, Richard Wiseman, William Cheselden, Percival Pott, John Hunter, Abraham Colles, Sir Charles Bell, John Collins Warren, Sir Benjamin Collins Brodie, Sir James Paget, Lord Lister, Sir Jonathan Hutchinson, Sir William Macewen, William Stewart Halsted, Henry Jacob Bigelow and James Marion Sims. This book will find good service in all libraries.

Caesarean Section: Lower segment operation. C. McIntosh Marshall. 230 pp. Baltimore: William Wood & Co., 1939. $6.50.

This book is an interesting, careful monograph on the low-segment method of cesarean section. It is well illustrated and clearly written, and there is an excellent bibliography after each chapter pertaining to the various parts of the operation. The author, however, has written nothing about postoperative treatment, a detail which, to the reviewer, is very necessary and important.

In the book sent for review there is an error in binding, which, if it holds throughout the entire edition, is a very serious defect. The price of the book seems a little out of proportion to its value.

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